GENEESS Guideline

Best Practices for Electronics in Medical Devices

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Contact

Filip Ponsaerts
Phone: +32 16 283412
Mobile: +32 474 921351
Filip.Ponsaerts@imec.be
IMEC
Kapeldreef 75
B3001 Heverlee

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The GENEESS Guidelines principle

The GENEESS Guideline is designed to provide all electronic medical device actors involved in design, qualification, industrialization and production practical guidelines to master the multi-disciplinary hardware aspects of active medical device realization and operation in a cost-effective way. The GENEESS Guideline is not an electrical nor product design guideline. The GENEESS Guideline provides the designer and medical device manufacturer the boundary conditions of industrial electronic manufacturing technology, basic operational reliability and regulatory requirements. It is intended to support the development of cost-effective, reliable medical devices with a short time-to-market requiring a minimum number of design iterations.

Some of the characteristics of the GENEESS Guideline are:

- The GENEESS Guideline is oriented towards the device realization and medical device reliability aspects within the regulatory framework.
- The GENEESS Guideline refers to the PBA DfM Guidelines of cEDM (www.cedm.be). These guidelines do not replace industrial standards but define or recommend what options in the standards to use and will fill in gaps when appropriate.

The information is not exhaustive. While every endeavor is made to ensure that the information is correct at the time of publication, the legal position may change as a result of matters including new legislative developments, new case law, local implementation variations or other developments.

GENEESS Guideline Scope

- The GENEESS Guideline is intended to be used for the realization of medical devices containing electronics.
- The GENEESS Guideline covers design and manufacturing of the electronic part of medical devices.
- The GENEESS Guideline includes basic elements of Design-for-X: Design-for-Test, Design-for-Reliability, Design-for-RoHS, etc.
- The GENEESS Guideline includes basic elements of regulatory requirements for medical devices.
- The GENEESS Guideline includes basic elements of project management for medical devices.
- The GENEESS Guideline includes a basic overview of biocompatibility for medical devices.

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imec contributors

Filip Ponsaerts
Maaike Op de Beeck

DSP Valley contributors

Frederik Horemans

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1. Applicable Documents

Interesting websites:
Official websites of national authorities regarding medical device safety.
http://ec.europa.eu/health/medical-devices/index_en.htm
http://www.fda.gov/MedicalDevices/default.htm
http://www.hc-sc.gc.ca/dhp-mps/md-im/activit/fs-fi/meddevfs_matmedfd-eng.php

2. Applicability of the GENEESS Guideline Best Practices

- The recommendations given in the guideline are intended to help the user in making choices that improve the manufacturability, reliability, testability, biocompatibility, etc., of the medical device. These recommendations are of a generic nature. Therefore, in specific cases more optimal solutions may exist.
- Design specification takes precedence over this guideline.
- The regulatory guidance in this document only covers the basics. Choices need to be made depending on the intended use of the medical device.

3. Motivation

Recently, the medical market has attracted attention from research institutes and electronic device manufacturers. This is not surprising: over the last decades, the reliability of electronic devices has improved drastically. Together with the continuous trend for miniaturization and for reduced power consumption seen in the electronics industry, electronic devices have become extremely suitable to solve medical issues. Moreover, based on the knowledge of IC fabrication, scientists have learned to extrapolate these fabrication processes in order to build very small reliable sensors, fluidic devices or devices with mechanical functions. The MEMS and microfluidic industry has learned how to successfully merge Si-based components with cheaper glass or polymer components. At this moment, conventional electronic chips can be combined with MEMS, microfluidic chips or sensors, opening the road for fabrication of medical devices able to sense, interpret and even act. Electronic engineers discover the medical world, and medical scientists discover electronics. New medical electronic devices are constantly under development and a myriad of opportunities are still open, since many medical conditions are still waiting for a well-designed, safe and effective electronic solution.

Nevertheless, developing an electronic device for the consumer market, the gaming world, etc. is very different from the developments needed to introduce an electronic device into the medical market successfully. Due to the large implications device failure can have in the medical world, these devices need to be very safe and effective, and hence severe premarket and post market surveillance from national authorities is standard for medical devices. In order to be successful in medical electronics, device safety and effectivity should be considered from the very first phase of development. Risk analysis and preventive/corrective measures are part of the early development stages too. This document has the goal to introduce the reader in the world of medical electronics, by providing an introduction to the special requirements for medical devices such as biocompatibility, sterilization and packaging of the device, the obligatory premarket approval process, risk analysis processes, and medical device testing for safety, including biological evaluation and MRI safety.

4. Introduction

A medical device is a tool which is used in order to diagnose, treat, cure or prevent a medical condition, or a tool used to improve the quality of life of people suffering from disabilities. The diversity of such devices is enormous and still growing due to the innovativeness of the medical device industry. Such devices range from small and simple tools such as a bandage or a thermometer, to more complex and invasive devices as implantable pacemakers, and highly complex large devices as MRI scanners. Such devices can be used in a hospital setting or at home, handled by trained medical personnel or by the patient himself or his relatives. Some tools can function without human interference, once installed/implanted, while others need permanent handling/follow-up by the caregiver or patient. Medical devices can be passive (hence no action is delivered, i.e. a thermometer) or active (i.e. a pacemaker).

Due to the very nature of medical devices, their use can have a strong impact on the health and quality of life of the user. Each device should bring benefits to the patient, and this without bringing the patient into unacceptable risks. No matter what kind of medical device is under discussion, the medical safety of the device is an unconditional demand. For complex devices such as an electronic implant, medical safety is one of the most important factors during the device development and production process.

To ensure user safety for all devices on the medical market, a medical device needs approval from the local national authorities before it can be sold. This regulatory framework for market access is organized by each country, i.e. by the *FDA* for the USA, by *Health Canada* for Canada, etc. Since the 1990ŝ, all countries in Europe follow the same regulatory framework, controlled by approved notified bodies in all EU countries. International harmonization of the procedures for market approval, essential for efficient development and market introduction of medical devices, is also seen in the global acceptance of various test standards such as the ISO10993 standard for biocompatibility testing of medical devices. After an approved device is introduced in the medical market, a strict post market surveillance procedure is applied in many countries, resulting in public information ranging from safety warnings and field alerts to device recalls when the device is not performing well regarding medical safety.

5. Approval process and the Medical Devices Directive

5.1. General approach of premarket approval processes

User safety is crucial for all medical devices, hence such a device needs approval from the local national authorities before it can be introduced to the medical market. This regulatory framework for market access is organized by each country, i.e. by the *FDA* for the USA, by *Health Canada* for Canada, etc. This national approval process makes market introduction costly and time-consuming, hence the need for more harmonization is obvious. Since the 1990ôs, all countries in Europe follow the same regulatory framework, controlled by approved notified bodies in all EU countries. Once the CE-label (hence approval) is given to a product, it can be sold in all EU countries. For other countries, international harmonization is seen in the global acceptance of various test standards for medical devices, such as the ISO10993 standard for biocompatibility testing of medical devices, which is accepted in most countries (although still minor differences in test requirements are present).

In most countries, the authorities giving approval to bring a product onto the medical market, will also apply a strict post market surveillance procedure, resulting in public information ranging from safety warnings and field alerts to device recalls when the device is not performing well regarding medical safety. Hence even after device approval, all medical device manufacturers should track the use of their products, being open for all complaints and remarks, and use this information for further enhancement of their existing devices, as well as for better design of new developments.

It is important to realize that a device manufacturer remains responsible for his medical devices, also after device approval. The manufacturer is defined by the FDA as ñthe natural or legal person with responsibility for the design, manufacture, packaging and labelling of a device before it is placed on the market under his own name, regardless of whether these operations are carried out by that person himself or on his behalf by a third partyò [1]. Hence the device manufacturer is also held responsible for device errors related to its suppliers, such as a change in production of subcomponents, a raw material change,... Moreover, the manufacturer is even responsible for foreseeable misuseôof his device, so reducing the change of misuse by smart device design is important. In spite of that, not all misuse can be prevented, and remaining foreseeable misuse should be considered during the product risk analysis of your medical device (see section 5.4.1. Risk analysis).

[1] Article 1 (2) (i) Directive 90/385/EEC as last amended by Directive 2007/47/EC, Article 1 (2) (f) Directive 93/42/EEC as last amended by Directive 2007/47/EC and Article 1 (2) (f) Directive 98/79/EC on in vitro diagnostic medical devices as last amended by Directive Regulation (EC) No 1882/2003.

Device classification based on intended use and on risk

Very important to obtain market approval and to carry out a correct product risk analysis, is the definition of the intended use of a medical device. Based on this intended use, the device will belong to one of the following international harmonized categories of medical devices:

1. Drugs
2. Devices for medical application (focus of this document)
3. Biologics for medical application (i.e. cells)
4. Combination products (combination of drug, device en/or biologics)
    - i.e. drug eluting stent: drug + device
    - i.e. scaffold with stem cells: device + biologics

For each of these categories, the test procedures for market approval are different.
In this document we will focus only on the category ódevicesô Be aware that a device can be a hardware device only, a software product only, or a hardware device combined with software.
Devices are further classified based on their risk, this classification is different between countries and defines the required risk assessment and test procedures. As an example, this risk classification and corresponding approval procedures for the USA and for Europe will be explained.

5.2. Premarket approval in the USA

The CDRH (Center for Devices and Radiological Health), a subdivision of the FDA, is controlling the medical devices (approval for market introduction as well as post market surveillance). Mission of the CDRH is to protect the health of the public by:

- ensuring market release of safe and effective medical devices.
- making sure that medical devices remain safe and effective.
- giving information and promoting the public health.

Based on their intended use and their risk, all medical devices are categorized by the CDRH into 3 classes [2]:

- Class I: very low to low risk
- Class II: moderate risk
- Class III: high risk (all implants are class III)

For each class, different approval procedures apply, with the most rigid approval procedure for highest risk devices. When a new device in developed, it will be classified by the CDRH based on intended use and risk. In case no medical devices with similar intended use/risk exist yet, the device will automatically be classified as high risk ï Class III, since no historical information is available to judge risk. In case it is obvious that this new device has a lower risk (advantageous for an easier approval process), the device can be placed in a lower risk class after going through the so called ôDe Novoô process.

If a product is labeled, promoted or used in a manner that meets the following definition in section 201(h) of the Federal Food Drug & Cosmetic (FD&C) Act it will be regulated by the Food and Drug Administration (FDA) as a medical device and is subject to premarketing and postmarketing regulatory controls.

Definition according to section 201(h) of the Federal Food Drug & Cosmetic (FD&C) Act:

- "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is: recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,
- intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
- intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes."

[2] Classification procedures: Code of Federal Regulations, Title 21, part 860 (usually known as 21 CFR 860)

Four types of premarket approval procedures exist:

1. Premarket Approval (PMA): most rigid control for devices with higher safety risk, takes max. 180 days for final approval decision, is the most expensive of the 4 approval methods.
2. Premarket Notification, also called 510k or 510(k): reduced procedure for approval, takes max. 90 days for final approval decision and is cheaper than a full PMA.
    a. for devices with low to moderate safety risk (Class I and II)
    b. for high risk devices (Class III) for which a "substantially equivalent" device is already approved by the FDA. Substantial equivalence means that the new device is at least as safe and effective as the predicate.
3. Exempt: for certain devices of Class I and II, no dedicated premarket approval is required due to very low risk of the device. Nevertheless, "general controls" are essential: the device needs to be listed and registered, it needs the correct labelling, and it should be proven that Good Manufacturing Practices (GMP) are applied for fabrication of the device.
4. Humanitarian Device exemption (HDE): approval for a device that is intended to benefit patients for a condition that affects fewer than 4000 individuals in the USA per year. For such small patient groups, the cost of a normal approval process would be too high, the device manufacturer`s R&D costs could exceed its market returns.

The FDA approves also "investigational device exemptions" (IDE) submissions. An IDE allows the manufacturer to use his investigational device in a clinical study to collect the required safety and effectiveness data for a PMA application or a 510(k) submission to FDA. For higher risk devices, the IDE approval process is more complex.
The FDA has a website containing lots of information, topics are well explained and all available for free. In case a non-American device manufacturer wants to get FDA approval, he needs first to appoint a representative living in the USA. This person should perform all FDA submissions, communications, etc. The FDA will help a manufacturer with his approval file, the FDA tries - with the help of the manufacturer- to check if a product is effective and safe and can be introduced into the medical market.

5.2.1. Quality System Regulation

Manufacturers must establish and follow quality systems to help ensure that their products consistently meet applicable requirements and specifications.
The quality systems for FDA-regulated products (food, drugs, biologics, and devices) are known as current good manufacturing practices (cGMPs).
cGMP requirements for devices are listed in part 820 (QSR 21 CFR part 820).

Because the regulation must apply to so many different types of devices, the regulation does not prescribe in detail how a manufacturer must produce a specific device. Rather, the regulation provides the framework that all manufacturers must follow by requiring that manufacturers develop and follow procedures and fill in the details that are appropriate to a given device according to the current state-of-the-art manufacturing for that specific device. Manufacturers should use good judgment when developing their quality system and apply those sections of the QS regulation that are applicable to their specific products and operations, 21 CFR 820.5 of the QS regulation.

Operating within this flexibility, it is the responsibility of each manufacturer to establish requirements for each type or family of devices that will result in devices that are safe and effective, and to establish methods and procedures to design, produce, distribute, etc. devices that meet the quality system requirements. The responsibility for meeting these requirements and for having objective evidence of meeting these requirements may not be delegated even though the actual work may be delegated.

It is left to manufacturers to determine the necessity for, or extent of, some quality elements and to develop and implement specific procedures tailored to their particular processes and devices.

The QS regulation applies to finished device manufacturers who intend to commercially distribute medical devices. A finished device is defined in 21 CFR 820.3(l) as any device or accessory to any device that is suitable for use or capable of functioning, whether or not it is packaged, labeled, or sterilized.
Certain components such as blood tubing and diagnostic x-ray components are considered by FDA to be finished devices because they are accessories to finished devices. A manufacturer of accessories is subject to the QS regulation.

Manufacturers of medical devices who want to sell their product in the US must meet the QSR regulations of FDA.

ISO 13485 is a global standard that is voluntary in the US
The Food and Drug Administration enforces 21 CFR 820.
21 CFR 820 is applicable to manufacturers of finished medical devices sold in the United States, including imported products.

5.3. Approval in Europe

Legislation has been established about the essential requirements a medical device must meet and this has been harmonised in a set of directives.

The technical specifications for products to meet essential requirements are laid down in harmonized standards. A product manufacturer is free to follow these standards or any other specification of his choice. However if a device manufacturer does deviate from harmonized standards, justification is needed to the satisfaction of the notified body (see later). Products compliant with harmonized standards benefit from a ñpresumption of conformityò

Medical devices must meet the Essential Requirements, are preferably assessed according to the harmonized standards and must achieve the specified performance levels.

The main directives applicable for medical devices (status January 2014):

- Active Implantable Medical Devices Directive (AIMDD): Directive 90/385/EEC covering active implantable medical devices modified by the directive 2007/47/CE
- Medical Devices Directive (MDD): Directive 93/42/EEC covering medical devices modified by the directive 2007/47/CE
- In Vitro Diagnostic Directive (IVDD): Directive 98/79/EC covering in vitro diagnostic medical devices
- Directive 2000/70/EC covering medical devices incorporating stable derivate of human blood or human plasma
- Directive 2003/12/EC on the reclassification of breast implants
- Directive 2003/32/EC covering medical devices utilizing tissues of animal origin
- Directive 2007/47/CE amends Directive 90/385/EEC and Directive 93/42/EEC

The directives are supplemented with medical devices guidelines (MEDDEV). These guidelines:

Åpromote a common approach by manufacturers and notified bodies
Åare intended for representatives of authorised authorities, Commission Services, notified bodies, industry and other interested parties
Åthese guidelines are not legally binding
Åthe guidelines are subject to a regular updating process

The directives and guidelines above provide the framework by which the manufacturer can make his choices. The directives are applicable depending on the function of the device and the application of this device.
The guidelines are not legal documents, but it is good practice (and appreciated by notified bodies) to follow their guidance.

Definition of medical device according to MDD 93/42/EC:

Any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software, intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation or compensation for an injury or handicap,
- investigation, replacement or modification of the anatomy or of a physiological process,
- control of conception,

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.

As an example, the distinction between a medical device and a customer gadget can be a thin line. A heart rate monitor intended to be used during sport, as an indication of performance of the training, can be considered a gadget. The same type of monitor intended to follow up on revalidation will be a medical device. The intended use of the apparatus will make the difference.

Definition of parties:

- ámanufacturerômeans the natural or legal person with responsibility for the design, manufacture, packaging and labelling of a device before it is placed on the market under his own name, regardless of whether these operations are carried out by that person himself or on his behalf by a third party.
- áauthorised representativeômeans any natural or legal person established in the Community who, explicitly designated by the manufacturer, acts and may be addressed by authorities and bodies in the Community instead of the manufacturer with regard to the latter's obligations under this Directive;

As you can see from above, the term ñmanufacturerò is not used as the party doing the physical production of the device, but more like the product owner. Company xyz who will place the device on the market under its name will be considered the ñmanufacturerò In many cases the actual manufacturing will be performed by a third party.
If e.g. a Japanese company wants to sell a medical device on the Benelux market, they will need an ñauthorised representativeò This is a person or company established within the Benelux.

The emphasis of the European legislation is placed onto the safety of the patient as well as the clinical condition. In the MDD 93/42/EEC this is described as:

> ñThe devices must be designed and manufactured in such way that, when used under the conditions and for the purposes intended, they will not compromise the clinical condition or the safety of patients, or the safety and health of users or, where applicable, other persons, provided that any risks which may be associated with their use constitute acceptable risks when weighed against the benefits to the patient and compatible with a high level of protection of health and safety.ò

Risk management on health and safety (illness and general) is a major concern in the legislation. Nor the patient, nor the caregivers, should be at unacceptable risks. The manufacturer must provide evidence of the right compromise.

In each EU country, a *competent authority* (CA) responsible for medical devices is appointed by the national government. ôNotified Bodiesôare private or public organizations accredited by the CA of an EU Member State to assess whether a product meets the MDD.

A device manufacturer will contact a Notified Body for premarket approval. This Notified Body can be located in any EU country, but it should be allowed to control the type of medical device under investigation, since not all Notified Bodies are accredited for assessment of all types of devices. Notified bodies shall be authorized to carry out inspections of manufacturers, during the premarket approval process as well as after market introduction (post market surveillance). Device manufacturers must provide the inspectors with all relevant information upon request.

While device manufacturers in the USA should interact with the FDA in order to perform the control/approval process as correctly and efficiently as possible, manufacturers are not allowed to interact regularly with the Notified Body to discuss the approval process.

Also in Europe, risk classes exist for medical devices, the classification differs slightly from that in the USA. The European classification depends on the duration of body contact, invasive character, use of an energy source, etc. ôMEDDEV 2. 4/1 Rev. 9: Classification of Medical devicesôdescribes in detail this classification, and its consequences regarding assessment of conformity with the MDDs.

- Class I, Is, Im: no risk to low risk devices, with Is for devices requiring sterilization and Im for devices measuring a function. No assessment by a Notified Body is required for class I, marketing is allowed purely by self-certification. For class Is or Im devices, self-certification is not allowed.
- Class IIa
- Class IIb
- Class III: highest risk (such as implants)

Obviously higher risk class devices need more rigorous device testing to get market approval, and such devices will receive more attention during post market surveillance.

5.3.1. Notified body

A notified body is a private organisation, operating in a competitive market. A medical device manufacturer is free in its choice of notified body for its regulatory compliance.

A notified body is nominated by a member state and can operate within the entire EU.
A notified body is also nominated based on designated requirements, such as knowledge, experience, independence and resources to conduct the conformity assessments.
Most of the notified bodies are specialized in specific subjects for medical devices.
The notified bodies are monitored by a member state through a Competent Authority e.g. in Belgium: FAGG / AFMPS / FAMHP (Federal Agency for Medicines and Health Products).

The choice of a notified body can be based on locality, specialisation, and experience. A starting point can be http://ec.europa.eu/enterprise/newapproach/nando/.

The notified body will assess the manufacturer's conformity to the Essential Requirements listed in the Directive (e.g. MDD, IVDD, and AIMDD).
Typical assessment methods are:

- Inspection (e.g. one batch)
- Quality assurance
- Type examination
- Design examination

A notified body can issue CE certificates and ISO 13485 compliance (quality system).
A notified body, nominated in Belgium, can next to assessments in Belgium, also work for e.g. a device manufacturer in the UK as well as an Authorised Representative for an overseas manufacturer.

It is strictly forbidden by Authorities that Notified Bodies give consultancy to manufacturers (due to conflict of interest).

Although Notified Bodies are not to deliver consultancy, they are open for discussion and guidance. They can in an early stage evaluate the choices a manufacturer makes. This guidance will however never be a replacement for consultancy.

5.3.2. CE marking

CE marking is a process in the EU region for several types of products put on the EU market.
For medical devices on the EU market, CE marking is required by law.
The labelling of products with CE indicates conformity with legislation.

For medical devices the CE marking states that the medical device meets EU essential requirements (safety and performance). These requirements have to be assessed before the medical device is being placed on the European Economic Area market (E.E.A.).

The intent of CE marking is to remove technical barriers to trade within the E.E.A. and guarantee the free movement of safe and performing products within the E.E.A.
Specifically for medical devices the applicable region for CE marking is extended with the EFTA countries (European Free Trade Association) and Turkey.

It is a criminal offence to label a device with CE in case it does not fully comply with legislation. The liability rests with the manufacturer.

A brief overview of the CE marking process:

1. Identify the **Directive(s)** that are applicable.
2. Choose the **conformity assessment procedure.**
3. Identify any **Harmonized European Standards** applicable (not mandatory, but implies presumption of conformity).
4. Determine if a Notified Body is required. Ask a proposal for certification.
5. Ensure to comply with all the **Essential Requirements.**
6. Maintain the **Technical Documentation** for the medical device. (see below)
7. Certification of the QMS and review of the Technical Documentation by the Notified Body (if applicable)
8. **Declaration of Conformity** and the supporting evidence.
9. Check that no other (purely) **national** requirements exist
10. Affix **CE marking** on your product

A first step in the CE marking process is to determine whether the product is a medical device according to the directives a listed in 3.1. This will be determined by the intended use of the product. (See above)

If it is a medical device, the classification of the device will show if a notified body is required in the CE marking process or not. (Annex IX of the MDD)
In case of a class I product (without measuring function), no Notified Body is required, the CE marking goes via self-certification.
The different classifications possible for a medical device:

- class I (low risk)
- class I with measuring function
- class I in a sterile condition
- class IIa (medium low risk)
- class IIb (medium high risk)
- class III (high risk)

For the Quality management System (QMS) see below. A typical route with a QMS is to comply with ISO 13485. (See also below). Note this is not the same, nor part of ISO 9001.

After all verification, certification and review activities needed for the CE process, the manufacturer has to issue a declaration of conformity. This underlines once more the liability of the manufacturer. Although other parties are involved (third parties for design and/or manufacturing, notified body, consultants,é), the manufacturer makes the sole decisions, based on the evidence available, to put the device on the market and declares its conformity.

When a notified body is involved, the final CE label will have a number, indicating the notified body.

5.3.3. Quality Management System

The medical device manufacturer must choose a conformity assessment procedure as described in the directive (annexes II to VII of the MDD). This choice can be influenced whether production will be high or low volume, or whether the product will be designed personally for the patient.
The intent of a QMS is to demonstrate the ability to provide medical devices and related services that consistently meet the customer requirements as well as the regulatory medical devices requirements. Furthermore the QMS helps to identify risks related to the process and the product and to control processes and interactions, market feedback and supply chain processes.

Annex II	Full Quality Assurance ï audits of the full QMS
Annex III	EC Type Examination ï type testing by the Notified Body
Annex IV	EC Verification, batch or 100% testing by the Notified Body
Annex V	Production Quality Assurance, audits of the QMS without design
Annex VI	Product Quality Assurance, audits of the QMS without design and manufacture

A quality management can be set up according to the harmonised standard EN ISO 13485:2012. Most organisations apply the ISO 13485 standard to achieve compliance. Note that organisations that meet ISO 13485 requirements cannot claim conformity to ISO 9001. ISO 9001 is not covered by ISO 13485 and must be certified separately.

Although ISO 13485 is not a requirement in many cases, it is considered good practice to set up a quality system in line with 13485.

5.3.4. Technical documentation

As part of the CE marking and the QMS, the product manufacturer is required to maintain a set of technical documentation per product type. (In case of personalised product, this might even be per product piece). The technical documentation shall reflect the status of a medical device at a particular moment in time.

This documentation should at least contain the items below:

1. Device description and product specification
2. Labelling (or draft labelling)
3. Design and Manufacturing Information
4. Essential Requirements Checklist
5. Risk management file
6. Verification and validation of the device
7. Required declarations (or proof if such a declaration is not possible)
8. Declaration of Conformity

5.3.5. Life cycle

The manufacturer is responsible for the product (quality and safety) throughout the complete lifetime of the device.

The manufacturer will manage the life cycle.
For the initial certification, the manufacturer will arrange for a review of the technical documentation and certification audit by your Notified Body. Depending on this review and audit, the manufacturer can affix the CE mark, or will need to resolve major and minor non-compliance first.
Periodically and at least once a year surveillance audits will be carried out by the Notified Body.
Next to this the Notified Body will periodically re-review the technical documentation at least once every 5 years.
The Notified body will carry out an unannounced audit once every 3 years. This will be at least one day with 2 auditors. For this the manufacturer must keep the QMS and technical documentation up to date at all time.
As a principle of good practice, the manufacturer will perform post market surveillance including post market clinical follow up (written down plan and record of results) and actively follow up on state-of-the-art for its products
Complaints and incidents are to be recorded and tracked in a CAPA system (corrective and preventative actions) and a recall plan has to be in place (severe incident).

5.4. Risk analysis and risk reduction by CAPA as part of quality management system

A device manufacturer has to invest in a good quality management (QM) system in order to ensure delivery of a safe and effective product. It is not only essential to prove the safety and effectivity of a medical product in order to receive approval for introduction on the market, a good QM system results also in a more efficient and hence cheaper device development, since product redesign in a later phase of the development can be limited or even avoided.

5.4.1. Risk analysis

Good QM starts with risk analysis, also called Failure Mode and Effect Analysis (FMEA) or product hazard analysis. Simple questions have to be answered: ñwhat can go wrong?ò and ñHow can we avoid these hazards?ò Nevertheless, providing correct and especially complete answers is not straightforward. First of all, a manufacturer has to look for possible risks during all phases in the lifecycle of the medical device: from design over development (R&D), transfer to production, manufacturing, sterilization, packaging, storage, up to post market use of the device, including implantation and active use of the device till its end of life. To get premarket approval for the device, most attention will go to the post market phase, but in order to develop an effective medical product for safe use later, risk analysis starts during the very initial design phase already.

When performing a risk analysis, one has to look for possible failures/hazards, but also for their probability (PRO), and the severity of the possible consequences/effects (SEC). Hence for each failure, the risk can be calculated as follows: RISK(failure) = PRO(failure) x SEC(failure). For all non-acceptable risks, solutions have to be found to reduce the risk, by avoiding the failure occurrence, and/or reducing the severity of the consequences. In case risk analysis is only performed at the end of the R&D phase or manufacturing phase, risk reduction might require severe product redesign. Hence it is of utmost important to start with a ópossibleôrisk analysis at a very early stage in the device development.

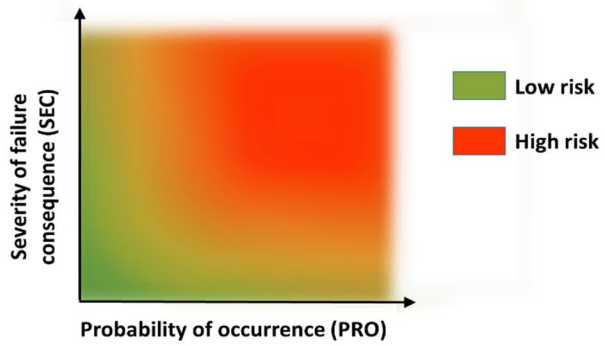


Fig. 5.1.: *For each failure mode, the risk is calculated as a combination of the probability of the failure occurrence and the severity of the failure consequence.*

When calculating the risk for all possible failures, several issues should be kept in mind:

- For a smooth premarket approval of the device, risks can only be accepted if they are low and if all measures are taken to reduce them, hence even small risks have to be avoided when possible.
- All failures have to be assessed: include "foreseeable misuse" in the risk analysis. Take so-called "human factors" into account: which behaviour of the user/care-taker/patient can be foreseen? What is "standard practice" in a hospital setting or by a patient at home when using similar devices? It might be that the new device under development has to be used in a different way compared to current similar devices, but due to the care-takers or patients habits misuse can be expected.
- Be aware that one should not assume that all device users have read the user's manual in great detail. Describing in a user's manual a possible risk / device failure mode, and how to avoid this failure, is not sufficient to conclude that the risk of the failure is reduced significantly. The same is true for labels: placing labels on a device to avoid a failure can be very useful but is not sufficient as protection for the user.
- Risks can be reduced significantly if failure detection is provided, e.g. if an alarm is warning the device user when using the device wrongly, or when the device can run a self-test which warns the user that a device failure is present.

5.4.2. CAPA

After performing a risk analysis, actions have to be taken to reduce all risks as much as possible, with most attention for the high risk failure modes. Most device manufacturers employ a so-called ôCAPA systemô(CAPA: corrective action / preventive action) as part of the QM system.

During the premarket phase:

Manage the quality of your design / fabrication by questioning and improving quality in all relevant domains during the device realization:

- Quality and reproducibility of raw materials, components,... hence question the quality of your suppliers.
- Control of own facility and equipment.
- Reliability of own processes (during fabrication, sterilization, packaging).
- If sterilization and packaging is not performed in-house: question the actions of the relevant third parties.
- Keep track of all fabrication processes and product batches by efficient and ôreadableô internal documents, track records,...
- If software is part of your medical product: question the quality of the software development too.

Since the legal responsibility of the final medical device is in hands of the device manufacturer, it is essential to control also the quality and reproducibility of the input of all involved companies (material and component suppliers, third parties for sterilization and packaging, contract manufacturers,..). Ideally, open discussions are held and the legal device manufacturer has a good understanding of the QM system (risk analysis & CAPA) of all involved third parties.

Post market phase:

After introduction on the medical market, a device will be tracked and reports on the device usage have to be made. For high risk medical devices (invasive for patients and/or lifesaving), even detailed tracking of each individual device is required by the competent national authorities who provided market approval to the device. Such device tracking might result in field alerts or even device recalls to ensure safe products are on the market, although smaller device issues can often be solved by device corrections performed by the device manufacturer. For devices with moderate to low risk, post market tracking might be stopped after an initial period during which the national authority is convinced about the safety of the device.

5.5. The use of IEC 60601-1

IEC 60601 is a series of technical standards for the safety and effectiveness of medical electrical equipment. It is published by the International Electrotechnical Commission and consists of a general standard, about 10 collateral standards, and about 60 particular standards.

The general standard IEC 60601-1 (Medical electrical equipment - Part 1: General requirements for basic safety and essential performance) contains general requirements. They are further explored in the series of standards.
IEC60601 is a widely accepted benchmark for medical electrical equipment. Compliance with the IEC 60601-1 International Standard and/or the relevant national version does not equal to medical device approval. However, it is a step towards medical device approval.

IEC60601-1 may be overridden or bypassed by the standards for a particular product. Collateral standards (60601-1-X) define the requirements for certain aspects of safety and performance, e.g. Electromagnetic Compatibility (IEC 60601-1-2) or Protection for diagnostic use of X-rays (IEC 60601-1-3).
Particular standards (60601-2-X) define the requirements for specific products, e.g. MR scanners (IEC 60601-2-33) or Electroencephalograms (IEC 60601-2-26).

For example, IEC 60601-1-9 for Environmentally Conscious Design of Medical Electrical Equipment is a collateral standard to IEC 60601-1. The Part 9 standard asks manufacturers of medical devices to consider the environmental impacts of their devices throughout the product's entire life cycle and to minimize these where possible.

The 3rd edition of IEC 60601-1 was published in 2005. The biggest upgrade in the 3rd edition is that Clause 4.2 requires a manufacturer to have a formal risk management process in place which complies with ISO 14971. The next biggest change is the introduction of essential performance into the scope.

STANDARD:	TITLE:
IEC 60601-1	MEE - Part 1: General Requirements for Basic Safety and Essential Performance
IEC 60601-1-1	MEE - Part 1-1: General requirements for safety - Collateral standard: Safety requirements for medical electrical systems
IEC 60601-1-2	MEE - Part 1-2: General Requirements for Safety - Collateral Standard: Electromagnetic Compatibility - Requirements and Tests
IEC 60601-1-3	MEE - Part 1-3: General Requirements for Basic Safety and Essential Performance - Collateral Standard: Radiation Protection in Diagnostic X-Ray Equipment
IEC 60601-1-4	MEE - Part 1-4: General requirements for safety - Collateral Standard: Programmable electrical medical systems
IEC 60601-1-6	MEE - Part 1-6: General requirements for basic safety and essential performance - Collateral standard: Usability
IEC 60601-1-8	MEE - Part 1-8: General requirements for basic safety and essential performance - Collateral Standard: General requirements, tests and guidance for alarm systems in MEE and medical electrical systems
IEC 60601-1-9	MEE - Part 1-9: General requirements for basic safety and essential performance - Collateral Standard: Requirements for environmentally conscious design
IEC 60601-1-10	MEE - Part 1-10: General requirements for basic safety and essential performance - Collateral Standard: Requirements for the development of physiologic closed-loop controllers
IEC 60601-1-11	MEE - Part 1-11: General requirements for basic safety and essential performance - Collateral Standard: Requirements for MEE and medical electrical systems used in the home healthcare environment
IEC 60601-2-1	MEE - Part 2-1: Particular requirements for the basic safety and essential performance of electron accelerators in the range 1 MeV to 50 MeV
IEC-60601-2-2	MEE - Part 2-2: Particular requirements for the basic safety and essential performance of high frequency surgical equipment and high frequency surgical accessories
IEC 60601-2-3	MEE - Part 2: Particular requirements for the safety of short-wave therapy equipment
IEC 60601-2-4	MEE - Part 2-4: Particular requirements for the safety of cardiac defibrillators
IEC 60601-2-5	MEE - Part 2-5: Particular requirements for the basic safety and essential performance of ultrasonic physiotherapy equipment
IEC 60601-2-6	MEE. Part 2: Particular requirements for the safety of microwave therapy equipment
IEC 60601-2-8	MEE - Part 2-8: Particular requirements for the safety of therapeutic X-ray equipment operating in the range 10 kV to 1 MV
IEC 60601-2-10	MEE. Part 2: Particular requirements for the safety of nerve and muscle stimulators
IEC 60601-2-11	MEE - Part 2: Particular requirements for the safety of gamma beam therapy equipment
IEC 60601-2-12	MEE - Part 2-12: Particular requirements for the safety of lung ventilators - Critical care ventilators
IEC 60601-2-13	MEE - Part 2-13: Particular requirements for the safety and essential performance of anaesthetic systems

IEC 60601-2-16	MEE - Part 2-16: Particular requirements for basic safety and essential performance of haemodialysis, haemodiafiltration and haemofiltration equipment
IEC-60601-2-17	MEE - Part 2-17: Particular requirements for the safety of automatically-controlled brachytherapy afterloading equipment
IEC 60601-2-18	MEE - Part 2-18: Particular requirements for the basic safety and essential performance of endoscopic equipment
IEC 60601-2-19	MEE - Part 2-19: Particular requirements for the basic safety and essential performance of infant incubators
IEC 60601-2-20	MEE - Part 2-20: Particular requirements for the basic safety and essential performance of infant transport incubators
IEC 60601-2-21	MEE - Part 2-21: Particular requirements for the basic safety and essential performance of infant radiant warmers
IEC 60601-2-22	MEE - Part 2-22: Particular requirements for basic safety and essential performance of surgical, cosmetic, therapeutic and diagnostic laser equipment
IEC 60601-2-23	MEE - Part 2-23: Particular requirements for the safety, including essential performance, of transcutaneous partial pressure monitoring equipment
IEC 60601-2-24	MEE - Part 2-24: Particular requirements for the safety of infusion pumps and controllers
IEC 60601-2-25	MEE - Part 2: Particular requirements for the safety of electrocardiographs
IEC-60601-2-26	MEE - Part 2-26: Particular requirements for the safety of electroencephalographs
IEC 60601-2-27	MEE - Part 2-27: Particular requirements for the safety, including essential performance, of electrocardiographic monitoring equipment
IEC 60601-2-28	MEE - Part 2-28: Particular requirements for the basic safety and essential performance of X-ray tube assemblies for medical diagnosis
IEC 60601-2-29	MEE - Part 2-29: Particular requirements for the basic safety and essential performance of radiotherapy simulators
IEC 60601-2-31	MEE - Part 2-31: Particular requirements for the basic safety and essential performance of external cardiac pacemakers with internal power source
IEC 60601-2-33	MEE - Part 2-33: Particular requirements for the basic safety and essential performance of magnetic resonance equipment for medical diagnosis
IEC-60601-2-34	MEE - Part 2-34: Particular requirements for the safety, including essential performance, of invasive blood pressure monitoring equipment
IEC 60601-2-36	MEE - Part 2: Particular requirements for the safety of equipment for extracorporeally induced lithotripsy
IEC 60601-2-37	MEE - Part 2-37: Particular requirements for the basic safety and essential performance of ultrasonic medical diagnostic and monitoring equipment
IEC 60601-2-39	MEE - Part 2-39: Particular requirements for basic safety and essential performance of peritoneal dialysis equipment
IEC 60601-2-40	MEE - Part 2-40: Particular requirements for the safety of electromyographs and evoked response equipment
IEC 60601-2-41	MEE - Part 2-41: Particular requirements for the basic safety and essential performance of surgical luminaires and luminaires for diagnosis

IEC-60601-2-43	MEE - Part 2-43: Particular requirements for the basic safety and essential performance of X-ray equipment for interventional procedures
IEC 60601-2-44	MEE - Part 2-44: Particular requirements for the basic safety and essential performance of X-ray equipment for computed tomography
IEC 60601-2-45	MEE - Part 2-45: Particular requirements for the safety of mammographic X-ray equipment and mammographic stereotactic devices
IEC 60601-2-46	MEE - Part 2-46: Particular requirements for the safety of operating tables
IEC 60601-2-47	MEE - Part 2-47: Particular requirements for the safety, including essential performance, of ambulatory electrocardiographic systems
IEC 60601-2-49	MEE - Part 2-49: Particular requirements for the safety of multifunction patient monitoring equipment
IEC 60601-2-50	MEE - Part 2-50: Particular requirements for the basic safety and essential performance of infant phototherapy equipment
IEC 60601-2-51	MEE - Part 2-51: Particular requirements for safety, including essential performance, of recording and analysing single channel and multichannel electrocardiographs
IEC 60601-2-52	MEE - Part 2-52: Particular requirements for the basic safety and essential performance of medical beds
IEC 60601-2-54	MEE - Part 2-54: Particular requirements for the basic safety and essential performance of X-ray equipment for radiography and radioscopy
IEC 60601-3-1	MEE - Part 3-1: Essential performance requirement for transcutaneous oxygen and carbon dioxide partial pressure monitoring equipment

6. Project Management Best Practices

Good project management supports good medical device practices. It fits your QMS (e.g. ISO 13485) and will support your technical documentation and evidence needed for CE marking.
Again the manufacturer is free to make his choices on what type or level of project management is used. We recommend that the items below are taken into account.

6.1. Design Control

Processes and procedures have to be established to ensure high Q, management and traceability of design from concept to finished product:

- Project plan
- Design requirements
- Design specification
- Design Documentation (Block diagram, internal signals, design choices, schematics, layout,é)
- V&V Test Specification (criteria and acceptance levels)
- V&V Test reports
- Risk assessments / FMEAs /Hazard analysis

Design control will ensure all levels of requirements for your medical device are well thought about (Essential requirements, customer requirements, patient safety,é) and tested. The risk assessments are key to support your evidence needed for CE marking the medical device.

6.2. Define the Scope and Objectives

Understand the project objectives. Making decisions on the real objectives will help you to plan the project.
The scope defines the boundary of the project, deciding what's in or out of scope will determine the amount of work which needs to be performed.
Understand who the stakeholders are, what they expect to be delivered and enlist their support. After defining the scope and objectives, get the stakeholders to review and agree to them.

As for any product, you have to make sure your medical device will meet the intended use for the intended public.

6.3. Define the Deliverables

Define what will be delivered by the project. Decide what tangible things will be delivered and document them in enough detail to enable someone else to produce them correctly and effectively.
Key stakeholders must review the definition of deliverables and must agree they accurately reflect what must be delivered.

6.4. Project Planning

Planning requires that the project manager decides which people, resources and budget are required to complete the project.
Define what activities are required to produce the deliverables using techniques such as Work Breakdown Structures. Estimate the time and effort required for each activity, dependencies between activities and decide a realistic schedule to complete them. Involve the project team in estimating how long activities will take. Set milestones which indicate critical dates during the project and write this into the project plan. Get the key stakeholders to review and agree to the plan.

Although not essential for your medical device, this will be essential to control your cost and time to market.

6.5. Communication

Project plans are useless unless they have been communicated effectively to the project team. All team members need to know their responsibilities.
Document product, design and project decisions.
You will need this for later references, defect and problem handling, as well as device certification (Technical file, design history file). Doing this during the project progress will save you a lot of problems and time.

Tracking and archiving your communication is part of your documentation for your medical device and might be reviewed by the Notified Body during audits. (CE marking and/or ISO 13485)

6.6. Tracking and Reporting Project Progress

Once the project is underway you must monitor and compare the actual progress with the planned progress. You will need progress reports from project team members. You should record variations between the actual and planned cost, schedule and scope. You should report variations to your manager and key stakeholders and take corrective actions if variations get too large.
You can adjust the plan in many ways to get the project back on track but you will always end up juggling cost, scope and schedule. If the project manager changes one of these, then one or both of the other elements will inevitably need changing. It is juggling these three elements - known as the project triangle - that typically causes a project manager the most headaches.

As stated at 4.4. Project management, although not essential for your medical device, this will be essential to control your cost and time to market.

6.7. Change Management

Stakeholders often change their mind about what must be delivered. Sometimes the business environment changes after the project starts, so assumptions made at the beginning of the project may no longer be valid. This often means the scope or deliverables of the project need changing. If a project manager accepted all changes into the project, the project would inevitably go over budget, be late and might never be completed.
By managing changes, the project manager can make decisions about whether or not to incorporate the changes immediately or in the future, or to reject them. This increases the chances of project success because the project manager controls how the changes are incorporated, can allocate resources accordingly and can plan when and how the changes are made. Not managing changes effectively is often a reason why projects fail.

As for any product, you have to make sure your medical device will meet the intended use for the intended public. For medical devices, it is imperative the project manager consults the stakeholders and medical decision maker with respect to the product changes, either requested or rejected.

6.8. Risk Management

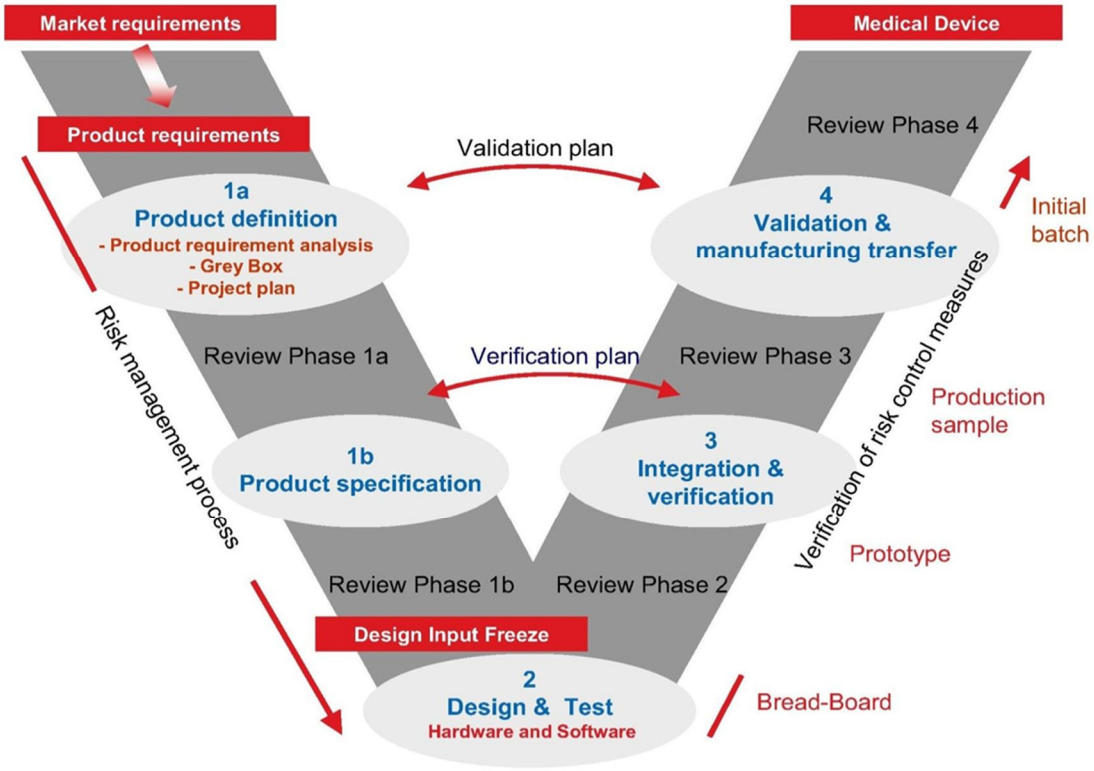
Risks are events which can adversely affect the successful outcome of the project. Risks will vary for each project but the main risks to a project must be identified as soon as possible. Plans must be made to avoid the risk, or, if the risk cannot be avoided, to mitigate the risk to lessen its impact if it occurs. This is known as risk management.
You will not manage all risks because there could be too many and not all risks have the same impact. So, identify all risks, estimate the likelihood of each risk occurring (1 = not likely, 2 = maybe likely, 3 = very likely). Estimate its impact on the project (1 - low, 2 - medium, 3 - high), then multiply the two numbers together to give the risk factor. High risk factors indicate the most severe risks. Manage the ten with the highest risk factors.
Constantly review risks and look out for new ones since they have a habit of occurring at any moment.
Not managing risks effectively is a common reason why projects fail.
Do not manage only direct product risks, but also external risks like changing legislation, standards & user requirements.

The risk assessments are key to support your evidence needed for CE marking the medical device.

7. Verification and validation

Verification is the process of checking whether the product adheres to the policies, standards, requirements,... The verification process should test the specified requirements, the product specification. Validation will check if the product fulfils its intended use in its intended environment, if it is what the customer wants. The validation process should test the product definition.

So verification should answer the question: Am I building the product right?
Validation should answer the question: Am I building the right product?



V&V activities are important because they:

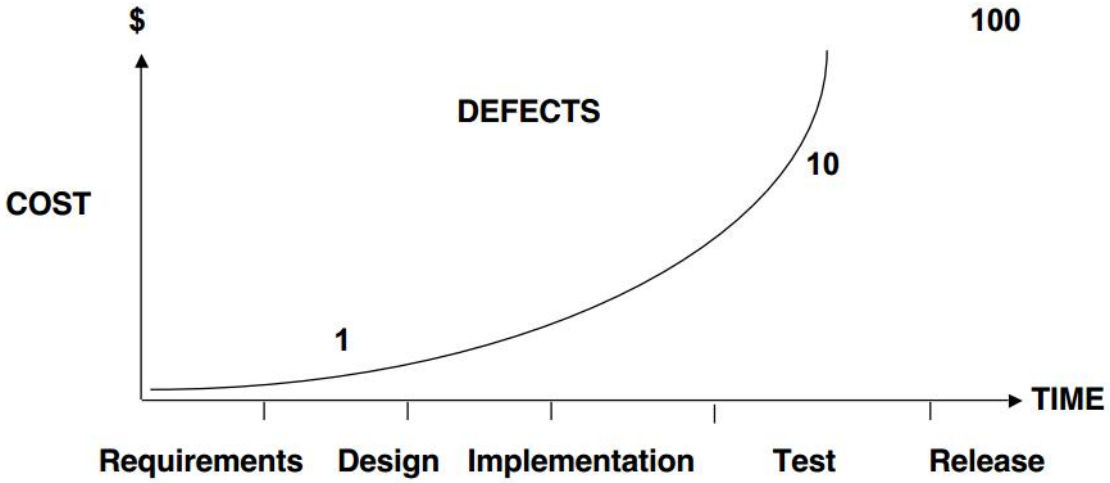
- Ensure the requirements are met.
- Remove defects from the product, reduce cost of poor quality and rework.
- Ensure the user's needs are met
- Improve the quality of product and process
- Improve productivity and performance

V&V is essential not only to ensure the customer requirements are met and you will deliver a product with the required quality, but also to ensure your medical device adheres to the regulatory requirements. It will give the manufacturer some of the needed evidence for the technical file and declaration of conformity.

V&V best practices:

- Remove defects and problems as early in the project as possible.
- Use (peer) reviews and inspections.
- Test at different stages in the design (module tests, regression tests, integration test).
- Test plans are based on product definition and specification, not on design and implementation.
- Adjust product definitions, specification and test plans as changes are approved by the stakeholders.
- Review changes.
- Use prototypes to pre-validate the product.

A typical figure of the cost to remove a defect/ problem versus the phase in the project:



8. DfX guidelines[3]

In the field of electronics design exists the concept of ñDesign-for-Xòto take into account the physical realization aspects of the PBA (Printed Board Assembly) like production methods, operations environment, failing mechanisms,é These are applicable for all electronic designs, so also for active medical devices incorporating electronics.

The points below do no cover the complete range of DfX, but give some basic design guidance for high level design deployable in the conceptual design phase. It is a good DfX practice reference for communication with customers and as such should be background knowledge for every manufacturer of active medical devices. For more in-depth information you can find guidelines at www.cedm.be.

8.1. Important when designing a Printed Board Assembly (PBA)

Although electronics have been around for more than half a century, design and production is not that straightforward. Letôs look at why a manufacturer of an active medical device should pay attention to DfX:

- Besides the realization of an electronic function for a medical device, a Printed Board Assembly (PBA) is a highly stressed (both at manufacturing and in operation, thermo-mechanically and other) complex **physical piece of hardware** which mandates proper Design-for-X to attain the required cost, quality, reliability and business objectives. (Remember intended use and safety.)
- A PBA and its function will involve a level of complexity. To support all the aspects of the PBA design, realization and implementation, the medical device manufacturer should invest in the appropriate amount of **PCB (Printed Circuit Board)/PBA technology knowledge** for all parties involved in PCB/PBA specification, design, industrialization, qualification, production, purchasing, quality control, installation and related management.
- **Low cost** manufacturing mandates **high yield** manufacturing. (e.g. cost of scrap, cost of field failures, risk and cost of medical device recall)
- The **impact of design** on PBA yield, cost, quality and reliability is at least one order of magnitude larger than the impact of manufacturing.
- Treat **Design-for-X aspects** of a PBA at the same level of importance as its functionality. A PBA design that does not meet functional requirements most likely will not create a profit. A poorly manufacturable, unreliable PBA design will create a loss. (e.g. cost of scrap, cost of field failures, risk and cost of medical device recall)
- **Designing a PBA** is more than PCB layout. It also includes PCB quality, material and process specification; component (BOM) selection and specification; assembly specification including materials, process flow and boundary conditions.

[3] PBA Design-for-Manufacturing Guideline, EDM-D-000, Good Design-for-X Practice, V1.0, July 2013, www.cedm.be

- There are limits to what can be assembled and interconnected per unit of area of a PBA. **High density interconnection** (an advanced technique) comes at the price of increased manufacturing cost and risks and reduced quality, reliability and delivery performance due to additional process steps and processes used at their performance limits. This needs to be acknowledged in the equipment design and when selecting high pin count and/or small pitch component packages.
- PCB and PBA technologies have **limited accuracy** regarding dimensional and physical properties. A good PBA design does not require better than 10% dimensional and physical property accuracy for the PCB.
- **RoHS compliancy**, lead-free and being lead-free solderable are three different properties of electronic components and parts. A lead-free solderable component might still contain lead. A RoHS compliant component might not be lead-free solderable.
- A **science based Design-for-Reliability** approach is the only viable way to realize long product lifetimes with sufficient confidence under given use conditions. ñReliabilityòtesting at board, module or system level cannot predict or guarantee the long lifetime requirement of professional electronics since:
    - The multitude of failure mechanisms present in a PBA under test have different acceleration factors. You will not find a magical accelerated test which will be able to cover all the different possible failures of electronics.
    - The experience-based extrapolation of environmental test results to real life conditions is obsolete due to the numerous material changes that have taken place in 21st century electronics. Too much has changed in materials and methods in a short time span.

*The electronics of an active medical device can involve a complex design. The device will be stressed during its intended use, yet has to comply with the (essential) requirements throughout its useful life. Due to legislation and new technologies the manufacturing and failure mechanisms have changed significantly. This can and will also impact medical device related items like field failures, risk for device recalls, patient safety, etc**é***
It is obvious a medical device manufacturer must pay attention to DfX

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8.2. Doôs and donôts of good DfX practice

The doôs and donôts below are a list of quick and relatively easy wins to come to a reliable and manufacturable active medical device. These are guidelines and can be deviated from, but only after careful consideration.

- **Provide sufficient room** for the PBAôs in the medical device assembly. Avoid exotic PCB form factors and shapes or exotic PBA constructions to accommodate for insufficient PBA space.
- **Keep the design simple** to minimize cost and maximize quality and reliability. Go for conventional PCB build-ups and component packages. Use only advanced (high density interconnection) technologies when mandatory and based on comprehensive quantitative argumentation.
- **Diversity** leads to increased costs and risks both in supply and in assembly. Minimize the number of component types per PBA.
- **Avoid ambiguity**. Specify all PBA aspects, verify and adhere to specification. Do not assume that ñexpertsò down the supply chain will make the appropriate choices for you. Lack of specification leads to non-quality, non-reliability, uncontrolled supply, product variability and finally unsatisfied customers.
- **Approve/qualify technologies**, PCB build-ups, components, materials, component-, PCB- & EMS-suppliers. Acknowledge that:
    - Not all that exists (components, PCB and PBA technologies, materials,...) is also suitable to be used in a PBA for a medical device.
    - PCB and EMS capability varies from supplier to supplier. Be selective in choosing a PCB and EMS supplier and qualify the supplier.
    - Critically evaluate all design choices including the validity of a reuse of previous design solutions.
- Always design for **machine assembly** and machine soldering. Manual work leads to high assembly cost, variable (low) quality and reliability risks. This might compromise your CE marking.
- **Adhere to design rules**. They are created to translate technological, manufacturing, quality, reliability, and other aspects of the PBA into tractable rules to facilitate efficient design of the physical PBA entity.
- Do not put all PBA **realization compromises** and complications at the manufacturing side. Consider electrical circuitry adaptations to fulfil Design-for-X requirements.
- Assess **PBA testability** early in design prior to PCB layout. Take care of Design-for-Testability (DfT) and Design-for-Repair requirements.
- Specify the **operational profile** of the PBA (environment and power cycling). Achieve product reliability by science based Design-for-Reliability (DfR).

8.3. Basic Design-for-Assembly rules

The list below contains design rules that affect the assembly of the electronics of an active medical device. Most common soldering techniques are wave soldering (a wave of hot liquid solder moving over the PCB) and reflow soldering (PCB goes through an oven, liquefying solder paste). Lead free soldering requires higher temperatures compared to lead containing (SnPb) soldering. Prior to soldering, the components are typically placed on the bare PCB with an automated placing machine.
These are guidelines and can be deviated from, but only after careful consideration. The guidelines and tool at the end of this section can be found at www.cedm.be

- Use **approved/qualified components**. The availability of components does not imply these are suitable for your assembly environment (nor for the essential requirements of your medical device for that matter) .
- Select components that lead to **low manufacturing error rates** and that fulfil operational profile based reliability requirements for your medical device.
- Limit the number of component types on PBA and per PBA side to reduce set-up cost as well as supply and set-up error risks at the assembly of your electronics. Use a specific component type only on one side of the PBA if the component count allows it.
- Take care of **BOM** (component) **assembly compatibility**.
    - Do not combine large, heavy components and small, high density component types on the same PBA. If necessary use daughter-PBA or separate PBA.
    - Avoid components with extreme dimensions: very small components (error rates, assembly compatibility) and very large components (coplanarity, reliability).
- Take care of **BOM** (component) compatibility with the **soldering processes**. The maximum thermal load of a component and the metallurgy of the components leads are key design parameters regarding compatibility with respect to lead-containing (SnPb) resp. lead-free soldering.
- Take care of lead-free soldering compatibility and via reliability of PCB. Select and specify **suitable PCB laminate material**. (PCB laminate is one of the base materials of a PCB)
- Design for **machine assembly and machine soldering**. Provide fiducials, component free areas and sufficient component clearance for automated processes. (Fiducials are physical markers needed for automated assembly)
- Select **PBA build-up and assembly sequence** early in design, prior to layout. In case of third parties for assembly of the electronics, involve them early.
- Minimize the number of **component placement runs**. (This is linked to the number of component types on your PBA and diversity of components)
- Put **everything on one side of the PBA** if this can be achieved without entering the domain of high density assembly. (at least one soldering step less)

  Exception: If there are through hole components on top and SMD (surface-mounted) components on the bottom, wave soldering only the bottom layer is sufficient.

- Do not place **through-hole components** on both sides of the PBA. This will make soldering extremely complex.

  Exception: press-fit connectors

- **Cluster through-hole components** to facilitate selective soldering. If selective soldering is needed, restrict it to one location.
- Avoid **wave soldering** large numbers of **SMD components**. Manufacturing error rate of wave soldering is ten times higher than that of reflow soldering for the same size of components.
- Use the **correct footprint design**. Do not combine footprints to accommodate different component types/sizes.
- **Specify assembly requirements**: IPC class, assembly materials, process boundary conditions (especially with process sensitive components), cleaning.

EDM Guidelines:

- EDM-D-001: PCB Specification
- EDM-D-002: Component Specification
- EDM-D-003: PBA Assembly Material Specification
- EDM-D-004: Design-for-Assembly

EDM Tools:

- Pred-X

8.4. Basic Printed Circuit Board (PCB) Design-for-Manufacturing rules

The list below contains design rules that affect the manufacturability of a bare PCB for an active medical device. A PCB constitutes of interconnected layers of conductive copper in the pattern needed for the tracks for interconnectivity, separated by insulating layers. The outer laminates will require a ñfinishòlayer to provide good soldering quality.
These are guidelines and can be deviated from, but only after careful consideration. The guidelines and tool at the end of this section can be found at www.cedm.be

- Use only **qualified PCB technologies and suppliers**.
- Select the **PCB laminate** material in accordance to the number of soldering steps including repair and PBA lifetime. (see also DfA rules above)
- Select **PCB finish** to provide good soldering quality. Give priority to interconnection reliability in PCB finish selection. (see EDM guideline below)
- Specify **quality requirements** (IPC class, IPC standards).
- Specify **moisture handling requirements** (IPC-1601 specification).
- Keep it simple. Use **conventional PCB interconnection** solutions. Use the simplest technology possible: lower cost, better quality, higher reliability.
- Use only **advanced PCB interconnection** features based on sound quantitative evaluation of their superiority over conventional solutions.
- Use the largest possible minimal track widths, track spacing, via land size and related features. (Lowest possible PCB density class)
- Only design **PCB layout features** using boundary (min/max) dimensions of the chosen density class where necessary. Use more relaxed dimensions whenever possible to improve yield (=cost), quality and reliability.
- Strictly obey **layout design rules.**
- Be critical about the need for **controlled impedance tracks**. (Advanced technique) Use it with restraint. Impedance requirements which require better than 10% accuracy exceed conventional PCB/PBA technology capabilities.
- Ensure a good **copper balancing**. Create a symmetrical PCB build-up to avoid warpage.
- Use **thermal relief** to connect vias for through-hole components to copper inner and outer planes
- Use thermal relief to connect SMD pads to copper planes.
- Design the **solder mask** pattern according to appropriate design rules, especially for solder mask defined pads, and verify its implementation.
- Do not **cover via holes** with solder mask when subsequent PCB finishing is needed to allow proper via cleaning in PCB manufacturing.

EDM Guidelines:

- EDM-D-001: PCB Specification
- EDM-D-005: Rigid PCB Build-Up and Density Classification

EDM Tools:

- PCB delamination and via lifetime calculator
- PCB laminate overview

8.5. Basic Design-for-Test rules

The list below contains design rules that affect the testability of an assembled PBA for an active medical device. Testing is needed to ensure verification and that the PBA out of the production facility is free of errors. Several test techniques exists, among them

- Boundary scan: uses functionality if available inside ICs.
- Automatic Optical Inspection: an optical inspection of components and soldering.
- Functional test: testing the functions of a PBA in order to test some degree of components.

These are guidelines and can be deviated from, but only after careful consideration. The guidelines and tool at the end of this section can be found at www.cedm.be

- Establish a **test strategy** based on PBA complexity, production volume, product value, customer expectations, troubleshooting efficiency.
- Make a distinction between testing to identify and repair **manufacturing defects** and Product Performance Verification (e.g. on customer demand).
- Whenever possible provide **test access** to all electrical nets (tracks, interconnects), preferably on a single PBA side, using test pads and/or vias with enlarged test lands.
- Provide **boundary scan testability** for PBA sections where test pads cannot be used.
- **Automatic Optical Inspection** (AOI) is not an alternative for providing electrical test access. The test coverage of AOI for interconnection defects is too low.
- **Functional test** used as a manufacturing test must be oriented towards component testing and fill the test coverage gaps left over by the structural tests. It is not a Product Performance Verification test aimed at product performance verification.
- Quantify **test coverage** and the probability of defective PBA slipping through for the test strategy chosen. Adapt if necessary.
- Know and agree upon what is tested and not tested in functional tests.
- Apply **Design-for-Repairability** rules if required. Allow for sufficient clearance between components.

EDM Guidelines:

- EDM-D-007: Quality and Test Coverage Quantification ï Design-for-Test

EDM Tools:

- Pred-X

8.6. Basic Design-for-Reliability rules

The list below contains design rules related to the reliability of an assembled PBA for an active medical device. This list is not exhaustive, it contains however some basic rules. These are guidelines and can be deviated from, but only after careful consideration. The guidelines and tool at the end of this section can be found at www.cedm.be

8.6.1. General

- Reliability is not absolute. Explicitly specify the **operational conditions** and the expected lifetime. Temperature cycling range and frequency are critical to reliability. The operating conditions are dependent on the intended use of the medical device.
- Acquire basic **knowledge** and understanding of PBA failure mechanisms. Understanding these mechanisms is key to the definition of good test plans for the medical device.
- Perform a **failure risk analysis** of the PBA early in design. Risk analysis is key for the evidence you need in the technical documentation to support the declaration of conformity. Also the earlier you can take actions to lower risks, the lower the time and resources involved.
- Provide sufficient **margin**. Lifetime cannot be determined accurately.
- Always select **lead-free soldering** compatible PCB laminates in case lead-free soldered PBA. Lead-free soldering will involve higher solder temperatures.

8.6.2. PBA subjected to strong thermal cycling

As mentioned in 8.6.1., temperature cycling and frequency are critical to reliability. The range, and speed it cycles (both in duty time, as well as the rate of temperature change) will trigger different failure modes in the electronics.

- Evaluate PCB **via reliability**. Select PCB laminate, adapt via design (diameter) and specify minimal plating thickness. (A via is the interconnect between at least two tracks or layers of copper in a PCB)
- Difference in coefficient of thermal expansion (CTE) between component and PCB is the main cause of interconnection failure (solder, conductive glue,é) . **Thermal stress** increases with the difference in CTE, the temperature range and the maximum temperature, component size and decreasing component stand-off. Therefore, in medical devices subjected to large or high cycle count thermal cycling avoid:
    - large ceramic and silicon (WL-CSP) based components;
    - large (>4mm) leadless components (QFN);
    - large TSOP with low CTE moulding compounds and/or Alloy 42 lead frames;
    - Partially populated plastic BGA with low CTE moulding compounds.
- Evaluate **solder joint reliability** of critical components. Contact component suppliers for solder joint reliability test data.

8.6.3. Mechanically stressed PBA: bending, vibration and shock

As mentioned above, temperature can induce mechanical stress which will trigger failure modes in the electronics of the medical device. Also direct mechanical stress will do this. Mechanical stress can be linked to the intended use of the mechanical device. It can occur through bending, shock or vibration. In case of shock and vibration, the Eigen frequencies are important (resonance).

- Evaluate **Eigen frequencies** of the PBA. Provide adequate fixation to push Eigen frequencies out of the mechanical loading spectrum. Fixation has to be determined as early as possible, preferably before final layout of the PCB.
- Only use PCB finishes that provide soldering to copper to avoid the brittle failure of a solder-Ni interface. (Do not use ENIG NiAu - as specific type of finish - in combination with lead-free soldering.)
- **Ceramic components** are susceptible to cracking under mechanical stress. Do not place ceramic components (e.g. capacitors) close to locations where strong bending may occur or take appropriate measures to avoid bending.
- Provide **mechanical fixation** (adhesive, corner bond, underfill) if all the above measures are insufficient. Note: this increases assembly cost. Fixation has to be determined as early as possible, preferably before final layout of the PCB.

8.6.4. Insulation reliability

Insulation is one of the top failures in medical device certification testing. (See chapter below, creep and clearance)
To improve insulation, handling and cleaning is key to avoid (ionic) contamination of the PCB and PBA of your medical device. To avoid contamination during operation, one can cover the device and/or PBA. On the PBA this can be done with a (conformal) coating.

- Specify **acceptable solder materials** (flux classes).
- Do not **cover via holes** with solder mask to allow proper via cleaning if post solder mask cleaning is required in PCB manufacturing or assembly.
- **Qualify PCB supplier** w.r.t. handling and cleaning.
- **Qualify EMS supplier** w.r.t. handling and cleaning.
- Maximize **electrical clearance** between closely spaced copper features to maximize surface insulation resistance especially on PCB for outdoor applications and where DC voltages are present.
- Avoid DC voltages on **closely spaced (≤1mm) vias** (e.g. in BGA footprints) to avoid CAF[4]. Select and specify CAF-resistant PCB laminates if necessary.
- Use **conformal coating** if condensation or debris may create insulation failure risk. Specify coating and cleaning requirements. Note that conformal coatings with voids at the PCB surface are worse than having no coating at all.
- Evaluate tin whisker risks. Specify acceptable component lead finishes and required tin whisker mitigation techniques and testing. (A tin whisker is tin thread of tin growing on the surface of tin containing material under specific conditions)

[4] CAF: Conductive Anodic Filament is a conductive path (semiconducting $Cu_2(OH)_3Cl$) formed at the epoxy-glass fiber interface under influence of moisture and electric fields which may create shorts between adjacent conductors especially closely spaced vias with a DC voltage bias.

8.6.5. BOM reliability (Bill of Material)

- Ensure use of the correct **component grade**. Suppliers might have medical grade tests for specific components.
- Use only **qualified components and component suppliers**.
- Make sure that all component features are the same (e.g. lead finish & quality) when using alternative components and suppliers.
- Do not use highly **moisture sensitive components**. Do not use components with an MSL value higher than 4. MSL=3 or lower is preferred.(this will impact your assembly process and might trigger failure modus during production)
- Avoid the use of **process sensitive components** that deviate from the J-STD-020 defined component soldering robustness requirements. If process sensitive components are present, specify assembly instructions.
  Critically evaluate the process sensitivity of all passive components especially the lead-free soldering compatibility: maximum temperature and time-above-liquid.
- Avoid highly **ESD sensitive components**. Provide PBA on-board ESD protection if necessary.

EDM Guidelines:

- EDM-D-001: PCB Specification
- EDM-D-002: Component Specification
- EDM-D-003: PBA Assembly Material Specification
- EDM-I-001: Mechanical Integration

EDM Tools:

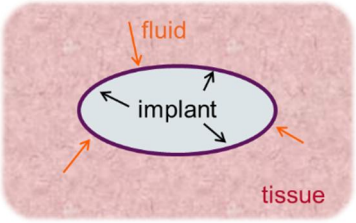
- FMEA tool: PBA failure risk assessment
- Via lifetime calculator

9. Biocompatibility, biostability and sterility issues for electronic devices

9.1. Implantable electronic devices

As mentioned already, medical device safety is a crucial issue. This results in special requirements for electronic devices which are used in close contact to the body, as is certainly the case with implantable devices. A human body is very different in nature from an electronic device. Consisting merely out of water, and containing many chemical components, human bodies damage electronics when direct contact exists: corrosion of electronics by body fluids will cause device failure. On the other hand, the human body will suffer from the presence of an electronic device too: diffusion of toxic materials from the electronic device into body tissue will cause local or systemic adverse effects. Since two very different worlds have to be combined, the so called *biocompatibility issues* deserve a lot of attention.

For passive devices consisting of only a few materials, biocompatibility can be realized just by selecting the proper materials: various materials are biocompatible, hence they do not cause an adverse reaction even when implanted in a human body during the intended usage period of the implant. Noble metals such as gold or platinum are such materials, as well as titanium which is used often for dental implants. But also some polymers such as polyimide or parylene are biocompatible and biostable for a considerable period of time. For electronic devices, the situation is more complex. The electronic core of the device itself contains always materials which are not biocompatible, such as copper. Furthermore, commercially available chip packages are not biocompatible, as well as conventional PCBs, soldermasks, glues... Hence diffusion of these toxic materials into the human tissue has to be prevented. Moreover, the electronic implant will function in a chemically aggressive wet environment, with the specific chemistry of the local tissue depending on the implant site. Leaking of body fluids into the electronic core of the device will result in device failure and should be prevented too. Hence an electronic device needs to be isolated from the body and vice versa by encapsulation of the electronic implant using barrier materials with strong diffusion stopping power for fluids and ions. Opposite to this, regarding to exposure to thermal variation and vibrations, the implant resides in a very easy environment, in contrast with other high-reliability electronics i.e. for space or automotive applications. As a result, a dedicated device package/encapsulation needs to be used for electronic implants.



Also essential for a medical implant is the *biostability* of the encapsulation materials. These materials should withstand their harsh bio-environment for the total implantation period. Materials should not degrade, in order to perform their intended function without failure. Note that in special cases, dedicated degradable coatings are applied on the outer surface of an implant. These coatings release a drug, a growth factor,... upon degradation. Such coatings are not biostable, they exhibit a well-controlled degradation process, and the degradation products will not harm the host tissue.

Even in case a fully biocompatible device is implanted, severe adverse effects might occur due to the bioburden (presence of bacteria) of the device. To avoid bacterial infections, implantation procedures have to be performed by trained medical personnel using high level surgical procedures, and the implanted device needs correct *sterilization* prior to its use, and. Hence the implantable system has to be developed such that common sterilization techniques can be applied without any device damage. In case the device is used many times after short contact with human tissue, exposure to many sterilization cycles should be feasible.

9.2. Wearable electronic devices

Wearable medical devices are used close to the body, but with less intense contact compared to an implanted device. Nevertheless, diffusion of moisture from the skin or ions through the skin occurs, which might result in adverse effects. A ósmart contact lensô(lens with electronics) will be in close contact to eye fluid and diffusion of toxic components into the body might occur, as well as leaking of fluid into the electronics. A ósmart pillô(small swallowable device i.e. with camera to investigate stomach or intestines) is not considered as an implant, although intimate contact with body fluids will occur. Hence biocompatibility, biostability and hermeticity with regard to the intended use of all these devices are important issues, and sterilization has to be performed prior to device usage. Always device development, optimization and testing has to be performed in view of the intended use of the device, and taking into account its type, duration and location of body contact, in order to ensure proper device functionality and efficacy, and user safety.

9.3. Natural bio-response of the human body upon implantation of foreign material.

Before discussing packaging approaches for implanted medical devices to make an electronic device and a human body compatible with each other, two major (problematic) issues related to device implantation need more explanation: (1) the foreign body reaction (FBR) which is the natural reaction from tissue upon an implanted foreign material, and (2) infection/biofilm formation, a risky complication which might occur after device implantation.
The ***Foreign Body Reaction*** (FBR) is the natural reaction from a body on the implantation of foreign material, starting from acute inflammation of local tissue and accumulation of monocytes/macrophages at the wound site. These white blood cells clean the wound area from debris and bacteria, but they also try to digest the implanted material, first as individual cells, later by fusing together to form so-called *foreign body giant cells*. Finally, after unsuccessful attempts of these foreign body giant cells to digest the implant, a dense layer of connective tissue is formed, walling off the implanted material/device from the body. This connective tissue will ensure mechanical anchoring of the implant, which might be advantageous. But for most implanted sensors, this walling off by connective tissue results in unreliable sensor measurements since the sensor surface is not in direct contact anymore with the soft tissue. Electrochemical sensors and pressure sensors will not function properly. For electrodes, this connective tissue enlarges the impedance of the electrodes, making the electrodes less sensitive to small biopotential signals are requiring a higher power consumption when a voltage shock has to be delivered.
Various factors modulate this FBR: the chemistry of the surface of the implant, the morphology, the porosity of the surface material, the mechanical properties,... all have an influence on the FBR. Currently, a lot of researchers investigate these complex relations in order to reduce the FBR.
In general, one can state that the more the implant material resembles the local tissue, hence the more biomimetic the material is, the milder the FBR.

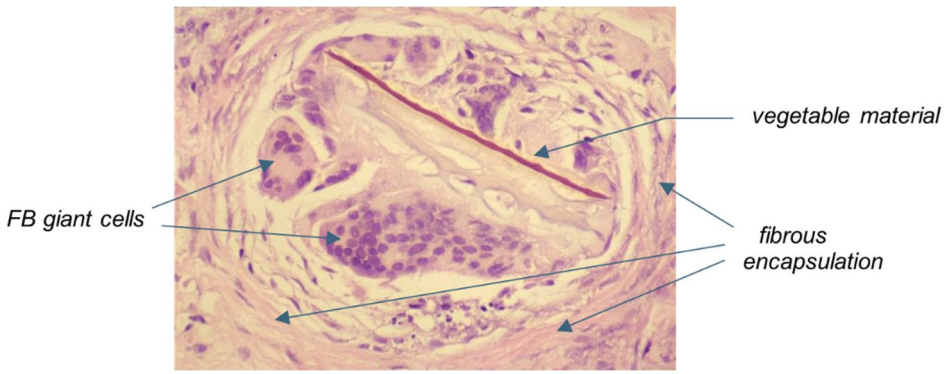


Fig. 9.1.: *Subsequent phases of the Foreign Body Reaction (source: Castner, D.G. and B.D. Ratner, Biomedical surface science: Foundations to frontiers. Surface Science, 2002, p. 28-60)*

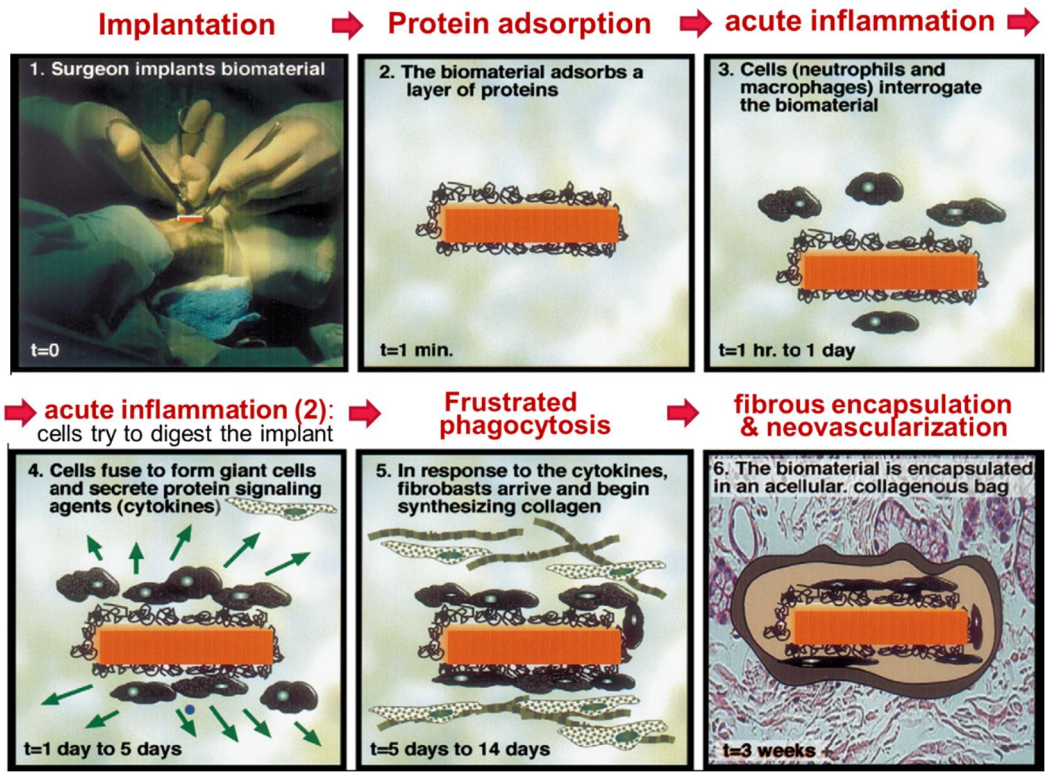

Implantation
Protein adsorption
acute inflammation
1. Surgeon implants biomaterial
t=0
2. The biomaterial adsorbs a layer of proteins
t=1 min.
3. Cells (neutrophils and macrophages) interrogate the biomaterial
t=1 hr. to 1 day
acute inflammation (2): cells try to digest the implant
Frustrated phagocytosis
fibrous encapsulation & neovascularization
4. Cells fuse to form giant cells and secrete protein signaling agents (cytokines)
t=1 day to 5 days
5. In response to the cytokines, fibrobasts arrive and begin synthesizing collagen
t=5 days to 14 days
6. The biomaterial is encapsulated in an acellular. collagenous bag
t=3 weeks

Fig. 9.2.: *result of Foreign body reaction after inhalation of vegetable material in lung: a fibrous encapsulation is formed to insulate the foreign material. The macrophages which fused to form foreign body (FB) giant cells are still visible (Picture source: www. granuloma.homestead.com).*

Infection upon implantation is a definitive risk associated with implants, causing a lot of problems and costs related to extra medication, longer hospitalization, and in a considerable amount of cases total removal of the implant. In spite of implant sterilization and stringent rules regarding prevention of infections in the operation room, bacteria might enter the body during implantation. White blood cells present in the implant area will try to clean up all debris and bacteria, but when sufficient bacteria are present, they might attach to the implant surface and form so called *biofilms*: bacterial colonies covering the implant surface. Such colonies are very difficult to destroy by antibiotics, hence prevention is of utmost importance.

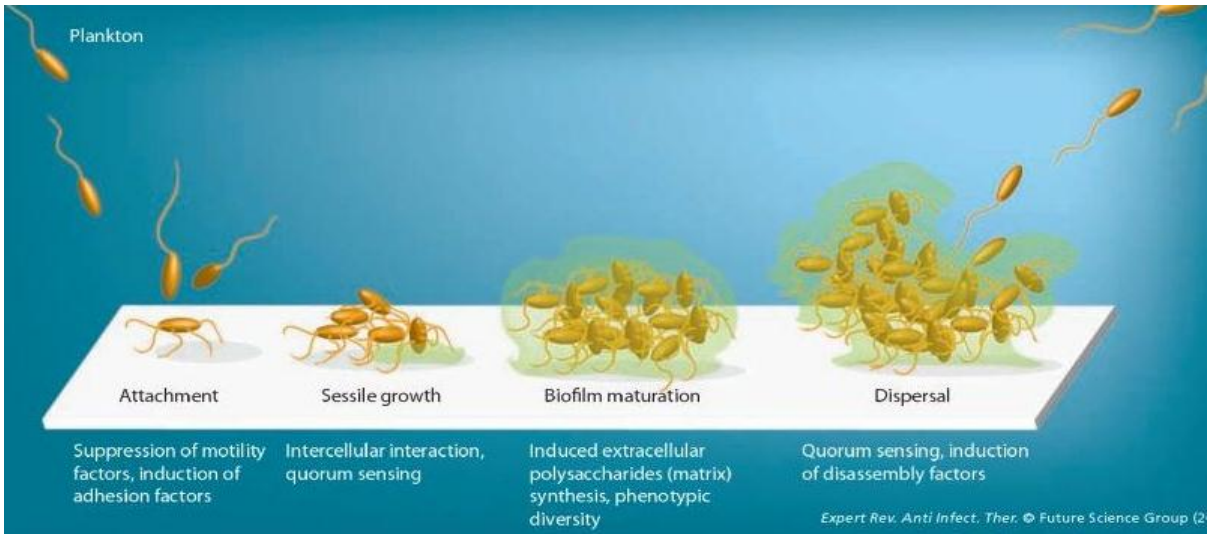

Plankton
Attachment
Sessile growth
Biofilm maturation
Dispersal
Suppression of motility factors, induction of adhesion factors
Intercellular interaction, quorum sensing
Induced extracellular polysaccharides (matrix) synthesis, phenotypic diversity
Quorum sensing, induction of disassembly factors
Expert Rev. Anti Infect. Ther. © Future Science Group (2

Fig. 9.3.: *development of a biofilm on a surface*
(Source: Expert Review Anti-infection Therapies ©2012 Expert Reviews Ltd.)

Various properties of the surface of the implant will strongly influence the risk of biofilm formation. As a general rule, one can state that an implant is less sensitive for biofilm attachment in case the local tissue cells have a strong affinity to attach and populate the implant surface. Surface roughness, used material and coatings, presence of antimicrobial drugs or cell growth factors, etc. will influence the affinity of healthy cells versus bacteria to attach and proliferate on the implant.

9.4. Biocompatibility and other material properties related to material-tissue interaction

Biocompatibility is the ability of a material or device to perform with an appropriate host response in a specific application[5]. In practical words, this means that a biomaterial does *not* evoke a toxic, allergic or immunologic reaction, it does *not* harm or destroy enzymes, cells or tissue, it does *not* cause thrombosis or tumours, etc. Note that biocompatibility is a contextual property, it is always related with the intended use of the material/device: a certain material may perform well for a short time in close contact with the skin, but may cause adverse effects after 24 hours implantation in muscle tissue. The statement that biocompatible materials do not initiate a tissue/body response or do not interact when implanted in biological tissue of a living organism, is clearly wrong! There is always a reaction upon implantation of foreign material (Foreign Body Reaction), but for biocompatible materials/devices, this reaction should be mild and limited in time.

A material/device used in the body should also be *biostable*: once implanted in the body, it should stay stable, i.e. no unwanted changes in mechanical or chemical properties of the materials should occur. For some applications: an external coating might be designed to be not bio-stable but bio-degradable (but degradation should be a well-controlled process!). Both biocompatibility and biostability are important properties of a medical device, hence in vitro and in vivo tests have to be performed to assure its biological safety, as part of the total risk management assessment of this device. More information about these tests can be found in section *11. Testing of electronic devices for medical applications.*

[5] Ratner, 2004

Some more properties regarding the interaction of a material with biological tissue are listed below:

- Bio-active or bio-functional material: a material is bio-active if it is enhancing certain (mostly beneficial) biological processes. A material can be bio-active by nature, or it can be made bio-active by loading it with a drug, a protein, a growth factor,...
- Antibacterial/antimicrobial material: the material reduces the risk on biofilm formation i.e. by active killing of bacteria (i.e. by release of dedicated antibiotics), or by promoting cell adhesion over bacteria adhesion.
- Biodegradable or bio-resolvable material: material is not biostable when implanted. Such materials are useful for drug delivery, or in case the intended function has only to be fulfilled for a limited time, after which degradation is an interesting alternative over explantation (i.e. degradable sutures, stents).
- Bio-mimetic material: a material is bio-mimetic if its shape, texture, composition mimics the tissue in which the material is implanted (goal: limit the foreign body reaction of the organism)
- Cytotoxic material: cells can't survive in close proximity of the material
- Cytophobic material: cells don't want to adhere to the material, although the material is not cytotoxic
- (bio-)Sterile material: a device should be sterile when implanted: it should be free of unwanted living organisms such as bacteria or fungal spores
- Bioburden: type and amount of bacteria present on a material or device
- Bio-safety of a device: (1) biocompatibility of the device, or (2) a medical active device should function well, dangerous defects of the device should be impossible ('safe failure mode').
- Biofouling: Biofouling or biological fouling is the accumulation of bacteria and other microorganisms, on wetted surfaces. A biofilm is the result of this biofouling process. Anti-fouling coatings are surface coatings applied to prevent biofouling.

9.5. Biocompatibility realized by dedicated encapsulation for implantable electronic devices

As mentioned before, the electronic core of an electronic device itself always contains materials which are not biocompatible, such as copper. Furthermore, commercially available chip packages are not biocompatible, as well as conventional PCBs, soldermasks, glues... It is impossible to replace all these materials with biocompatible alternative materials. Hence biocompatibility of an electronic device for implantation, needs to be realized by separating very well the device from the host. This is realized by the device packaging or encapsulation, which should give the required mechanical support, but should also prevent diffusion of toxic materials from the electronic core into the human tissue, as well as avoid any leaking of biofluid inside the device itself.

Due to these very special requirements for packaging an implantable system, and due to the diversity of the implanted devices, various dedicated packaging technologies are used or currently under development.

Implantable electronic devices such as pacemakers or cochlear implants are traditionally packaged in a rigid Titanium (Ti) box to ensure hermetic and biocompatible packaging of the microelectronic device. Such a Ti-box is a well-known and safe package for implants, since the Ti shell is an excellent diffusion barrier and dedicated high temperature welding techniques are developed to ensure a hermetic closure of the Ti-package. In order to protect the electronic core during the high temperature welding, this Ti-box is often large compared to the conventionally packaged electronics inside. Consequently, during implantation a larger insertion wound is needed resulting in a more pronounced Foreign Body Reaction (FBR) and a higher infection (biofilm) risk upon implantation. Also irritation and limited user comfort are more likely due to the strong mismatch between the soft body tissue and the rigid Ti-box [6] [7]. Also, for specific applications, a flexible and/or stretchable device might be needed or local optical transparency might be essential, obviously the traditional Ti-box based package cannot provide such properties.

In the past, ceramic materials have been used successfully as diffusion stopping encapsulation for electronic implants, with the advantage that high welding temperatures resulting in larger implants are avoided. However, due to its brittleness, a ceramic package is prone to cracks and breakage upon impact, making this encapsulation approach less popular. Recently Valtronics introduced a new implantable packaging approach based on glass.

[6] J. M. Anderson, Annu. Rev. Mater. Res., Vol. 23, pp. 81-110, 2001.
[7] G. Kotzar, M. Freas, et al, ñEvaluation of MEMS materials of construction for implantable medical devicesò, Biomaterials, 23, 2002, pp. 2737-2750.

Recently, due to the myriad of implantable devices currently under development, a whole variety of packaging solutions is heavily researched, each to solve the specific needs of the implant. Polymer based bi-direction diffusion barriers and polymer encapsulations are gaining popularity [8] [9]. Biocompatible polymers are developed, with interesting properties regarding diffusion stopping power, elasticity, biostability, optical transparency, etc. In addition, various materials with antibacterial properties are under development, enabling the application of a dedicated coating to an implant to reduce the risk on biofilm formation. These materials are antimicrobial in nature or they release antimicrobial products/drugs.

[8] Maaike Op de Beeck, et al., ñBiostability and corrosion resistance of a biocompatible encapsulation and interconnect technology for implantable electronicsò, Proc. Of 45th Intern. Symp. on Microelectronics, San Diego, USA, Sept 2012
[9] Maaike Op de Beeck et al, ñImproved chip & component encapsulation by dedicated diffusion barriers to reduce corrosion sensitivity in biological and humid environments.òEMPC 2013, September 9 - 12, Grenoble; France

10. Device cleaning, sterilization and packaging of medical implants

A device for medical applications should not only be biocompatible in case it is in contact with the human body, it should also be sterile prior to usage. Hence after manufacturing, severe device cleaning is required. If the intended use of the device includes direct contact with a human body (wearable or implantable device), device cleaning is followed by sterilization and dedicated packaging to maintain the sterility during transport and storage. For some sterilization techniques, a dedicated package is used first, followed by a sterilization process which is active through the package material. This approach eliminates the risk of device contamination during a final packaging step.

In case sterilization of the device is essential, all materials used in the device should allow at least one common sterilization technique. The 3 most used types of sterilization (and with well-known effects, interesting for smooth premarket approval) are the following:

1. Radiation based techniques (Remark that exposing active electronics to radiation might be a challenge!).
    a. Gamma radiation (most common, highest penetration)
    b. Electron beam radiation
    c. X-ray radiation
2. ETO sterilization: Chemical treatment by ethylene oxide (ETO), a very toxic gas to which the device is exposed. The treatment is performed at room temperature, making this technique very suitable for most polymers. Due to the high toxicity of ETO, this technique is only performed by dedicated companies (in service mode), typically for devices needing only one sterilization treatment (e.g. implants).
3. Autoclave sterilization: steam treatment at elevated temperature (>100° C): this technique is most used in hospitals for repetitive sterilization of medical tools. Tools should withstand high temperatures.

Also under development are new alternative sterilization techniques such as treatment by hydrogen peroxide, ozone, nitrogen dioxide and supercritical carbon dioxide (esp. interesting for combinatorial devices, e.g. devices coated with a protein containing material, or a sensor loaded with proteins). These techniques are gaining popularity, but the rationale behind the use of these alternative techniques should be given during the premarket approval process. Since sterilization and sterile packaging are very specific processes, device manufacturers will often use a specialized company (subcontractor) to perform these final process steps on their devices.

As a final remark, be aware that some medical devices are sterilized more than once. Hence when the effect of sterilization on your device materials has to be tested, consider all sterilization treatments as cumulative. Example: 3 times a gamma radiation of 20 kGray (dose) has the same effect as 1 radiation of 60 kGray, a dose which should be acceptable for all your device materials.

10.1. Development of medical devices

The development of a device for the consumer market differs in various aspect from the development of a medical device, due to its high importance and possibly severe consequences for the user. Due to this, extensive device testing is crucial, to ensure the (bio-)safety and effectiveness of the device. The testing protocols are partly similar to electronic device testing for the consumer market, although typically more rigorous testing is performed, and for devices in close contact with the human body special dedicated testing is needed regarding biocompatibility and MRI safety (for implants). To ensure all devices on the medical market are properly tested and hence biosafe, all countries have a regulatory framework in place, controlling premarket approval and post market device follow-up. In Fig. 10.1. an overview of the development phases of a medical device is shown. The various development phases can overlap somewhat in time, due to re-iterations of the device design to improve safety and/or effectiveness.

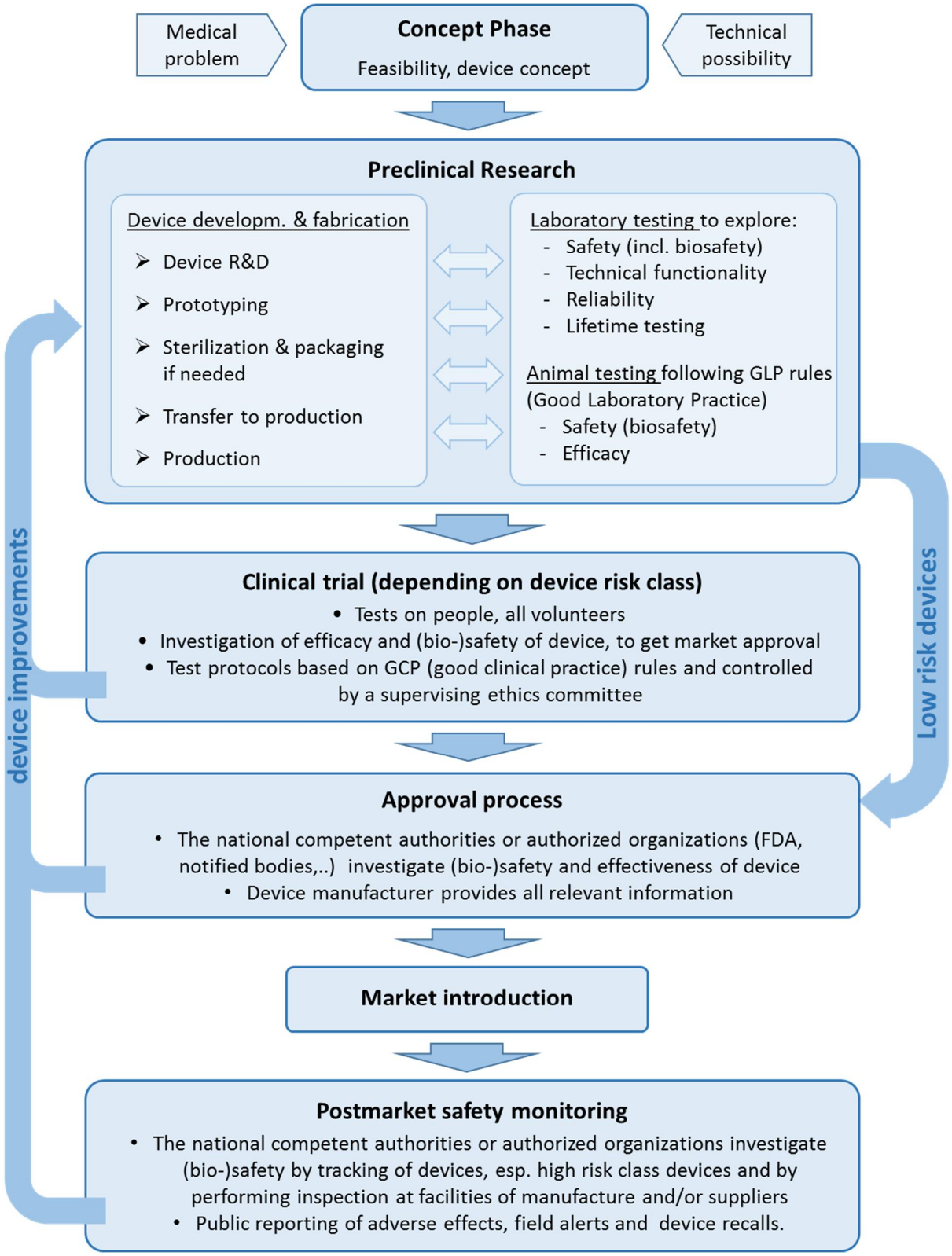

Medical problem
Concept Phase
Feasibility, device concept
Technical possibility
Preclinical Research
Device developm. & fabrication
Device R&D
Prototyping
Sterilization & packaging if needed
Transfer to production
Production
Laboratory testing to explore:
- Safety (incl. biosafety)
- Technical functionality
- Reliability
- Lifetime testing
Animal testing following GLP rules (Good Laboratory Practice)
- Safety (biosafety)
- Efficacy
Clinical trial (depending on device risk class)
• Tests on people, all volunteers
• Investigation of efficacy and (bio-)safety of device, to get market approval
• Test protocols based on GCP (good clinical practice) rules and controlled by a supervising ethics committee
Approval process
• The national competent authorities or authorized organizations (FDA, notified bodies,..) investigate (bio-)safety and effectiveness of device
• Device manufacturer provides all relevant information
Market introduction
Postmarket safety monitoring
• The national competent authorities or authorized organizations investigate (bio-)safety by tracking of devices, esp. high risk class devices and by performing inspection at facilities of manufacture and/or suppliers
• Public reporting of adverse effects, field alerts and device recalls.
device improvements
Low risk devices

Fig. 10.1. : *Various phases of medical device development*

In other sections of this document, various aspects of these development phases are discussed in more detail.

11. Testing of electronic devices for medical applications

Testing of a device for the consumer market differs in various aspects from the test protocols for a medical device. First of all, very extensive testing is crucial, to ensure the (bio-)safety and effectiveness of the device. Secondly, next to technical functionality tests, an evaluation of the biological safety of the device should be performed, which is an extensive task in case the device is in close contact with the human body during usage (hence for wearable or implantable devices). Finally, due to the regulatory framework which exists in each country, all these device tests should be performed following certain (inter)national approved practices, and they should be reported in detail, in order to get permission to bring the device on the medical market.

11.1. Technical functionality and reliability tests

When testing the technical functionality of a medical device, one should start from well-known test protocols for electronics for the consumer market. A myriad of test standards and guidelines exists for electronic devices in general, but most of these documents are not dedicated towards medical devices. Hence often testing is performed by using test protocols developed for so-called õhigh-reliabilityô devices, e.g. for automotive or space applications. But the concept õhigh reliability deviceô is strongly dependent on the intended use of a device, hence testing of such devices too. Tests for endurance towards harsh vibrations, long term exposure to temperatures up to e.g. 400°C, extensive thermal cycling tests,... are all rather useless for wearable or implantable devices. Such devices need to be tested for temperature/shock/vibrations etc. for a period corresponding to transport and storage of the device only. Further testing should be performed taking into account the special environment of the device, e.g. a chemically harsh, wet environment with a rather constant temperature around 37°C for implants. Furthermore, accelerated testing to predict failures and the device lifetime, is typically performed by testing under elevated temperature conditions. This kind of tests is sometimes impossible or useless for medical devices, since they contain materials (polymers, proteins,..) which degrade at higher temperatures, while these materials will serve their function perfectly at 37°C.

The need for more dedicated standard tests for electronic implants is clearly existing. Some research groups spend severe efforts to address this gap. The International Electronics Manufacturing Initiative (iNEMI) is an R&D consortium of ~100 leading electronics manufacturers, suppliers, associations, government agencies and universities. iNEMI roadmaps future technology requirements of the global electronics industry, identifies and prioritizes technology and infrastructure gaps, and helps eliminate those gaps through dedicated projects. For the medical market, the iNEMI consortium partners identified a clear gap regarding dedicated test protocols for reliability and safety evaluation of medical electronics. To address this gap, two projects have been started: (1) õQualification Methods for Portable Medical Productsô and (2) õReliability Requirements for Implantable Medical Devicesô. Both activities will result in various publications/presentations, including a white paper available for a broad public on the iNEMI website (expected publication date: end of 2014) [10].

[10] iNEMI website: http://www.inemi.org/focus/medical-electronics

Currently, a device manufacturer should derive his test protocols from existing standards and guidelines to test electronic devices, but these standards/guidelines should be evaluated critically, and adjusted appropriately towards the intended use of the medical device. When device testing is performed using deviations from an existing test standard, the authorized authority for medical market approval should be informed very well about the motivation of the test deviations.

11.2. Biocompatibility testing / biological evaluation of device

For medical devices in close contact with the human body such as wearable and implantable devices, special dedicated testing is needed regarding biocompatibility, sometimes also called the ôbiological evaluation of a deviceô Both biocompatibility and biostability refer to the interaction between a medical device and the local tissue of the patient as well as his total physiological system. In vitro (cell culture) tests as well as in vivo (animal) tests have to be performed to assure biological safety of the device.

11.2.1. History and need for harmonization

The first biocompatibility standard was the USP (US Pharmacopeia) class qualification, a procedure needed to receive FDA approval for a medical device. Only later, in 1987, the Tripartite Agreement introduced the concept of biocompatibility testing being focused on type of contact between device and tissue (Guidance Memo G87-1). In 1995, the FDA replaced the Tripartite Agreement by the Blue Book memorandum G95-1, adopting the ISO 10993 as standard for biocompatibility testing. The applied ISO tests tend to be more stringent than the USP tests, hence tests according to the ISO 10993 standard are requested by the FDA. Although the ISO 10993 standard is currently accepted worldwide, for the FDA extra testing is sometimes needed (see table 11.1). Also for some domains in the Japanese medical market, the required test procedures are slightly different from the ISO or USP tests.

11.2.2. Current test standards for biocompatibility testing

Information and recommendations about such total risk management process for medical devices can be found in ISO 14971, and in ISO 10993 part1. The ISO 10993 standard is a long document, consisting of 20 subparts, all describing a variety of test protocols and decision criteria (part 3 till part 20), while part 2 discusses lab animals welfare requirements. It is important to realize that ISO 10993 is not a strict set of tests with clear and binding pass/fail criteria, due to the very different nature and purpose of the various medical devices. As explained already, biocompatibility is a contextual concept: material/device requirements will differ substantially depending on the type of contact made with the human body, the duration of this contact, etc. Hence testing for biological safety might be very different from device to device. ISO10993-part 1 elaborates on designing the correct test schedule for each type of device, as is shown in table 11.1 (copied from ISO10993-part 1).

A first and very important biological test performed on all devices/materials used on/in a human body are in vitro cytotoxicity tests, described in ISO 10993-part 5. Also some other tests in ISO10993 are based on in vitro cell culture testing. In vitro tests are popular in order to limit animal testing to an absolute minimum. Nevertheless, the limitations of in vitro testing compared to real implant situations are important.

Regarding pharmacokinetics: in vitro assays are usually very different from in vivo situations regarding exposure time, metabolism, tissue penetration, clearance and extraction.
Regarding metabolism: many non-toxic substances become toxic after being metabolised by the liver, and many substances that are toxic in vitro may be detoxified by liver enzymes

Regarding tissue response: a toxic response in vitro may be measured by changes in cell survival or metabolism, while the major problem in vivo may be a tissue response.

In view of both animal welfare and patient safety, investigations are performed to test biological safety of materials/devices on cell cultures using primary cells and on tissue cultures. These tests are valid for premarket approval if their rationale is explained, but they can not (yet) completely replace animal testing ie. for implantable devices.

Medical Device Categorization by Contact Duration			Biological Effect											
			Initial Evaluation Tests								Supplementary Evaluation Tests			
Nature of Body Contact		**A - Limited** (≤ 24 hours) **B - Prolonged** (24 hours-30 days) **C - Permanent** (> 30 days)	Cytotoxicity	Sensitization	Irritation or Intracutaneous Reactivity	Systemic Toxicity (acute)	Subacute and Subchronic Toxicity	Genotoxicity	Implantation	Hemocompatibility	Chronic Toxicity	Carcinogenicity	Reproductive/Developmental[3]	Biodegradation[3]
Category	Contact													
Surface Device	Skin	A	●	●	●									
		B	●	●	●									
		C	●	●	●									
	Mucosal Membrane	A	●	●	●									
		B	●	●	●	F	F		F					
		C	●	●	●	F	●	●	F		F			
	Breached or Compromised Surface	A	●	●	●	F								
		B	●	●	●	F	F		F					
		C	●	●	●	F	●	●	F		F			
External Communicating Device	Blood Path, Indirect	A	●	●	●	●				●				
		B	●	●	●	●	F			●				
		C	●	●	F	●	●	●	F	●	●	●		
	Tissue/Bone/Dentin[1]	A	●	●	●	F								
		B	●	●	●	●	●	●	●					
		C	●	●	●	●	●	●	●		●	●		
	Circulating Blood	A	●	●	●	●		F[2]		●				
		B	●	●	●	●	●	●	●	●				
		C	●	●	●	●	●	●	●	●	●	●		
Implant Device	Tissue/Bone	A	●	●	●	F								
		B	●	●	●	●	●	●	●					
		C	●	●	●	●	●	●	●		●	●		
	Blood	A	●	●	●	●	●		●	●				
		B	●	●	●	●	●	●	●	●				
		C	●	●	●	●	●	●	●	●	●	●		

1: tissue includes tissue fluids and subcutaneous spaces
2: for all devices used in extracorporeal circuits
3: depends on specific nature of the device and its component materials

Table 11.1: Biocompatibility test matrix (to be used only as guideline for the development of a safety assessment for a medical device) indicating tests advised by ISO 10993 (●, and additional testing (F) which might be needed for FDA approval (Source: Pacific Biolabs)

11.2.3. Note about the USP In Vivo Biological Reactivity Tests (Class I-VI Plastics Tests)

As stated before, for FDA approval of a medical device, ISO testing is essential. Hence *USP classification* for materials has no legal value anymore. Nevertheless, for materials, esp. for polymers, USP tests are still popular, since this USP classification for materials remains useful for potential customers who are looking for materials to fabricate their devices, or for users of products in laboratory settings, for which no FDA approval is needed.

11.2.4. Tests regarding sterilization and sterile packaging

For devices in close contact with the human body during usage, sterilization prior to device use is essential. Since sterilization is most often performed immediately after device fabrication, a sterile package is essential to ensure the device remains sterile during transport and storage. Packaging and sterilization are typically outsourced by the device manufacturer to dedicated companies. Directives and standards for cleaning, packaging and sterilization exist and are well-known by these companies. These documents are obviously dedicated towards medical devices, hence they provide a clear guidance, without room for confusion or uncertainties.

11.3. MRI safety issues

Wearable devices typically do not cause major problems during MRI procedures, since they can be removed from the body during the MRI procedure. In the special case a life-saving device has to be removed during MRI, a dedicated medical specialist should be present during the procedure, in order to give the correct medical treatment in case the patient encounters severe problems.

Implantable devices cannot be easily removed and they might cause various (serious) problems during an MRI investigation, as listed below:

- An MR system uses a static magnetic field (typical magnetic field strength 1.5T or 3T), and superposes a gradient electromagnetic field to enable 3D imaging. The static magnetic field is very strong and can induce a static force (hence displacement) or torque on both active and passive implants, in case implant materials are (weakly) magnetic. Hence even weakly magnetic materials implanted in soft tissue are not safe for a patient during MRI procedures the first 6 weeks after implantation. About 6 weeks after implantation the Foreign Body Reaction (tissue ingrowth, scarring) has provided sufficient incorporation of the implant into the tissue, and hence an MRI procedure is not causing a device displacement anymore. An MRI investigation can be performed directly after the implantation for weak magnetic material which is fixed rigidly in the body (e.g. by bone screws,...).
  In case of subcutaneous implants, the movement of magnetic material during an MRI procedure can sometimes be limited by using special bandages which hold the implant in place.
- The gradient RF field in an MRI system produces a movement of electrons (hence electronic current) in all conductors, which might produce (potentially dangerous) heating of these conductors. These conductive loops can consist of implanted materials (e.g. pacemaker leads and guidewires), but also the human body is sufficient conductive, and the high frequency of the RF field allows that energy is even passing through small insulating areas in the loop. For certain lengths of conductive loops, resonance effects can occur which create high currents causing very severe heating. Hence implanted devices need carefully designed current pads to avoid heating during MRI, just electrically insulating the implant from the patient will not be sufficient to avoid all risk on heating. MRI specialists from their side will take all preventive measures to avoid long loops are formed by the body (placement of insulation between arms, legs

and body,...). For subcutaneous implanted devices which produce mild heating, the patient can be covered locally with cold packs or wet bandages to absorb the heat generated during MRI tests.

- Certain medical implants will stop functioning or will malfunction during MRI tests, but they will not be damaged. Such implants have to be switched off during MRI testing, but they can be switched on again after the MRI procedure. Other types of implanted device might be damaged during MRI and should not be switched on afterwards (or no MRI procedure should be performed to safe the device).
- Materials which are (weakly) magnetic will disturb the magnetic field during MRI tests, hence artefacts (imaging defects) are generated, which might result in unclear images making a diagnosis impossible. Conductive loops carrying (weak) currents during MRI cause artefacts too. In such cases MRI tests should not be performed since the tests will not deliver useful information to the medical specialists.

MRI safety labelling.

In order to assess the safety of an implant for a patient during an MRI procedure, dedicated tests should be performed at specialized labs, in case (weak) magnetic material or conductive material is present in the implanted device. These tests will result in the appropriate device labelling:

- Materials being non-magnetic and non-conductive are safe to use during all kind of MRI tests, hence they are labelled as ôMRI-safeô
- As explained above, for certain implants an MRI test is only safe under dedicated conditions. Such implants are labelled as ôMRI-conditionalô, and conditions for safe MRI use should be indicated by the device manufacturer.
- Regarding the labels ôMRI safeôand ôMRI-conditionalô, one should realize that the meaning of these labels is redefined in 2005 (ASTM F2503). The old label ôMR-compatibleôis confusing and should not be used anymore.

Valuable information regarding MRI safety can be found at the website of the Institute for Magnetic Resonance Safety, Education and Research (IMRSER): www.imrser.org .

12. Avoid product certification testing failure[11]

This section lists some of the major product certification failures for medical devices. When a product has to be reworked because it fails to conform to the standard, it often results in costly delays. By detecting these errors early in the design and manufacturing stages, you can help your device get to market on time and on budget.

This section lists the ten most common failures, gives some explanation as to why they occur, and offers tips on how to avoid them from the beginning.

Note: All clause numbering used in section refers to IEC60601-1 unless otherwise indicated.

12.1. EMC failure

The most frequent source of problems for Electromagnetic Compatibility (EMC) is related to the Radio Frequency Emissions being broadcast by the Equipment Under Test (EUT).

EMC is defined as:

> *The ability of an equipment or system to function satisfactorily in its electromagnetic environment without introducing intolerable electromagnetic disturbances to anything in that environment or being disturbed itself by an external influence in that environment.*

The most common design errors causing EMC problems are:

- Using generic components not specifically designed for medical devices.
- Not making good metal-to-metal contact around enclosures.
- Large holes in enclosures.
- Using plastic enclosures around very ñoisyòcircuits.
- Ground wires that are too long and not large enough to be of a low impedance.
- Electrostatic discharge (ESD) to membrane switches, keyboards, monitor bezels, etc.

12.2. Creepage and clearance distances

A large percentage of medical devices that are under evaluation have problems with creepage and clearance distances (C&Cós) and/or the insulation provided within the device or between parts of the device. Errors with creepage and clearance distances will usually result in redesign and delays in getting to market.

Creepage and clearance distances are related to both working voltage (peak) and the required level of insulation. In essence, when the working voltage increases, the distance between conductors of circuits must also increase to prevent currents flowing over the surface of insulation (creepage) or between circuits through air (clearance).

[11] Intertek testing services, March 2012

EMC and C&C problems normally require significant redesign.
It is not difficult to achieve the correct C&C distances, dielectric withstand and insulation type. The five fundamental reasons for errors are as follows:

- Å The definition of the type of circuit was not understood. This typically occurs where the working voltage has been incorrectly defined by the manufacturer during the design phase.
- Å The type of insulation that was needed was not understood.
- Å The component was not evaluated prior to designing it into the equipment.
- Å The differences between Information Technology Equipment and Medical Equipment Standards were not understood.
- Å The standard was not available when designing the equipment.

12.3. Indicator colours

Despite IEC 60601-1 clearly stating that the colour red on equipment is for exclusive use to indicate a warning of danger and/or a need for urgent action, red indicator lights are often used for indication purposes. There is an exclusion for dot-matrix and alphanumeric displays (e.g. 7-segment displays), which are allowed to be red. However, any other function using LEDs or lamps must be a colour other than red.

Additionally, yellow (or amber) indicators are often inappropriately used where green lights should be used.

12.4. Transformers and PSUs

In over 70% of cases, we find that there is a problem with transformers and power supplies. Unlike other product types, medical devices tend to be tested more severely. One of these tests is the Overload Test: each winding is loaded as normal until the transformer reaches thermal equilibrium; thereafter, each winding is overloaded in turn. If a transformer is wound for 60 Hz, it usually overheats badly at 50 Hz (but not the other way around).

Medical device standards have more stringent construction requirements for transformers. Many of the transformers tested fail due to their construction, including:

- Å Insufficient creepage and clearance distance between windings
- Å Inadequate insulation between windings and between windings and the core
- Å Unapproved materials used for the construction

Very few switching power supplies are designed specifically for use in medical devices. Many are sold as õmedically approved,òbut this usually means that the PSU is an adaptation of one built for Information Technology equipment. The leakage current may be acceptable, but the isolation required from the mains to low-voltage is usually lacking, causing the manufacturer of the PSU to put a disclaimer in the use instructions or data sheet such as õNot suitable for use with equipment having a direct patient connection.ò

12.5. Wiring cross-sectional area

Somewhere in most medical devices, the cross-sectional area wiring (insulated or printed wiring) is too small for the circuit into which it is connected. The same dimensions apply for Printed Circuit Boards (PCBs), which is frequently overlooked, especially where outputs for power are provided (AC or DC). The wires coming off a connector on a PCB could be compliant, but the traces to the female connector on the PCB are frequently undersized. This means that the pins of the connector on the PCB and the traces connecting to the connector will heat up, possibly resulting in an open circuit and failure to reliably perform as intended. If the nominal voltage multiplied by current is 15 Watts or more, this represents a fire risk.

12.6. Colours of ground (earth) wires

Manufacturers of large equipment with multiple earth connections (grounding connections) are frequently non-compliant with Sub-clause 6.5, which defines the colours for earth conductors. The colours of ground wires for medical devices have been globally standardized to Green/Yellow where the single yellow stripe constitutes 40% of the total surface.

We see many variations on this, such as all yellow with a green stripe, green with two yellow stripes, and so on. In general, identification by green and yellow insulation must only be used for:

- Protective earth conductors (see sub-clause 18 b).
- Any insulation on conductors inside equipment which connect accessible metal parts or other protectively earthed parts with a protective function to the protective earth terminal. These shall be identified by the colors green and yellow at least at the termination of the conductors.
- Potential equalization conductors (see sub-clause 18 e).

Conductors connecting to either protective earth or functional earth should be green and yellow. We often see incorrect colors being used for grounding purposes.
Green and yellow are distinctive and help prevent conductors from being placed in the wrong position. Protective and functional earth are distinguished from each other by different markings; see also Clause 18.

12.7. How to avoid these failures

Why do these errors happen in the first place? Often, design engineers do not have copies of the standard(s) they need to meet. They tell us that they ñdesign to the specificationògiven to them by marketing, or the edition or revision of the standard they followed is out of date. Pressure to cut costs and get to market faster also have their effects, resulting in the selection of components that will not adequately integrate into a medical device.

One way to avoid these failures is to perform a full and detailed risk analysis of the intended use of the device, including an EMC risk analysis based on the modes of operation. Start the risk analysis before starting the design; it will call up most hazards based on the intended use and the indications for use. Redo the risk assessment at regular intervals to make sure your design is addressing the risks.
Designing your device using a risk-based model usually means that the device will be compliant.

Here are some other simple steps you can take to improve your success rate:

1. Seek assistance from qualified sources early in the design cycle. For example, call your test lab for a design review. You will be able to see what is needed and keep that information for future products.

2. Qualify the components you intend to use. Do not take the salesmanôs word for it ï ask him to prove that the component is ñmedically approved.ò

3. If you are using an autorouter for PCB layouts, ensure that you have set the correct creepage and clearance values and do not accept the defaults. Check the plots for errors before committing to production.

4. Ensure that the wiring you use is the correct type and rating for the circuit it will be connecting to.

5. Always ensure that circuits are protected with an overcurrent protection device of a suitable type and rating, and where possible, certified. Thermal protection devices used in transformers must be Certified Components; otherwise, several weeks of additional testing will be required.

6. Buy copies of the standards and extract the tables that apply to your product (this saves a lot of time flipping backwards and forwards).

7. Using the tables you extracted from the standards, clearly define the required elements for compliance in the design specification. This may sound simple, but very few do this. Those that do can save themselves thousands of dollars in rework.

8. Produce an isolation diagram and discuss this with your test lab. This will save you time and money when doing conformity assessment testing.

13. Development of safe and effective medical devices: use other people's experience

13.1. Learn from the failures of others

FDA's "Medical Device Recall Report"[12], published by CDRH's Office of Compliance, shows that the total number of recalls almost doubled from FY 2003 to FY 2012 [13]. This increase in medical device recalls might suggest that recent medical devices are less safe, but this is probably not the case. First of all, the medical device industry is growing, and this growth is still faster than the increase in device recalls. Secondly, there is a growing awareness regarding device safety, and a better device tracking/reporting. This results in an increased amount of device recalls, but that does not mean that the medical market became more unsafe, on the contrary.

Device recalls are mostly the consequence of adverse effects on patients, sometimes with a severe outcome for the patient. Hence nobody is happy with a device recall. But such device recalls, as well as field alerts and warnings from national authorized organizations, are not only essential to ensure safe products are on the medical market, they are also very instructional for all device manufacturers, since these warnings and recalls can contain very useful information regarding device safety in general. Indeed, learning from the errors of others is a very interesting way to improve the safety of your own devices. Keeping an eye on public safety information of devices similar to your own devices, is certainly what a smart manufacturer should do. But also the general overall trend regarding device recalls is interesting and might warn device manufacturers for certain risks during device development.

13.2. Use outsourced manufacturing for unknown process steps

Device manufacturers should outsource device manufacturing steps they are not familiar with. Device cleaning, sterilization and packaging are typical manufacturing steps which are outsourced, but also steps during development might be outsourced. For each medical device, FDA approval/CE labelling etc. is essential. This procedure is difficult, costly and time-consuming, hence in case of lack of experience in this approval procedure, outsourcing should be looked at already in an early phase of device development. Finally during device development, a lot of testing is involved. For tests in unknown areas, such as biosafety tests for an electronic device manufacturer, outsourcing is essential. Look for certified labs for such tests in view of the later premarket approval process.

Obviously outsourced partners should be selected very carefully, since the final responsibility of a medical device is with the manufacturer, not with the subcontractors or suppliers. But using the knowledge of an experienced partner will lead easier to success than trying something a device manufacturer is not familiar with.

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12 http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHTransparency/UCM388442.pdf

13 Stephen Levy, http://www.qmed.com/news/medical-device-recalls-growing-slower-pace-industry

13.3. Avoid most common failure modes

When looking at device failures, a lot of them can be categorized in a few failure modes, resulting in the following advice:

Analyse very well the medical problem which should be solved by the device under development. Too often contacts with the final device users are present during the initial device concept phase, but they are lost during further device development. These contacts are important regarding the knowledge of the human factors, as well as to address correctly the medical needs.

Human factors are important.
Typical ways of performing a medical procedure, typical habits in the medical world,... it is all important to prevent device and treatment failures. A device manufacturer should invest in learning to know all stakeholders - the patients, the hospital wards, the nurses and doctors, etc. - and their standard work procedures.

Outsourcing of device manufacturing steps or testing is crucial if a device manufacturer has no relevant experience.
Especially start-ups with limited experience should look for outsourcing possibilities. Contract manufacturers and suppliers should be selected very carefully, since the national competent authorities will always consider the device manufacturer as responsible for his device. If possible, use contract manufacturers which have experience in the fabrication/testing of similar medical devices.

Human errors remain an important concern.
- Human errors are possible during device development manufacturing, sterilization and packaging, hence a good quality management system is essential, with an efficient error tracking system in order to perform a correct root cause analysis followed by preventive actions after error detection.
- Human errors occur also during device usage, a safe device can result in adverse effects when used wrongly by patients or caregivers. A very clear user manual and device labelling is essential. Take care of good translations of user manuals.

Test, test, test!
A lot of testing is involved during device development, varying from extensive technical functionality tests and (bio-)safety tests, to clinical trials on human volunteers. Start testing very early in the device development. Perform tests on materials and components of your device, on subsets of your device, etc. to shorten the time-to-market of the final device. Perform tests as much as possible in a standardized way and keep track of all test results, this information will be essential for a faster premarket approval process.

14. Medical devices to comply with hazardous substances restrictions

As of July 22th 2014 the substance restrictions of the RoHS Directive are applicable to medical devices. Medical devices have so far been exempt from RoHS, which requires the elimination of lead, cadmium, mercury, and other substances from electronics, but they will now fall under the scope of RoHS Recast (RoHS2, EU Directive 2011/65/EU). In vitro diagnostic medical devices will be required to comply with hazardous substances restrictions as of July 22th 2016. Only active implantable medical devices remain outside the scope of RoHS requirements for now.

Since the RoHS Recast Directive has come into action in 2011, RoHS is now a CE-marking directive. This means that if you manufacture an electrical/electronic product, device or equipment, you can no longer CE-mark in accordance with just the Medical Device Directive MDD (or Machinery, EMC or Low Voltage directive for that matter). Compliance with the RoHS directive is required before you can place the CE mark on your product and this should be clear on your Declaration of Conformity.

Compliance with the requirements of the EU RoHS2 Directive requires manufacturers to adhere to the conformity assessment procedures presented in Annex II of EU Commission Decision No. 768/2008/EC:

> *ñThe manufacturer shall establish the technical documentation. The documentation shall make it possible to assess the product's conformity to the relevant requirements, and shall include an adequate analysis and assessment of the risk(s). The technical documentation shall specify the applicable requirements and cover, as far as relevant for the assessment, the design, manufacture and operation of the productò*

Although there still are exemptions to the regulation under specific circumstances, regardless of inclusion or exemption, manufacturers must demonstrate that their equipment has been designed and manufactured in accordance with the requirements set out in RoHS, prepare the required technical documentation, and implement the internal production control procedures in line with the directive. RoHS does not only impact your supply chain as your suppliers must provide RoHS compliant components and (sub)assemblies (for which you need proof from your supplier). It impacts your own procedures like procurement and logistics, and most of all design and manufacturing.

With respect to the transition for products in case they currently are not RoHS compliant, according to RoHS2, stocks of spare parts designed for these products (placed on the market before July 22th 2014) can still be used for repair, reuse(refurbishment), updating of functionalities and upgrading of capacity of medical devices. Non-RoHS spare parts and components for the above listed activities can be manufactured and sold after July 2014 (but cannot be used on new RoHS compliant equipment). You will need to have proper traceability in place to prove prior/past July 2014 manufacturing and selling.

15. Conclusions

Recently, medical problems are addressed more and more by electronic devices. Conventional electronic chips are combined with MEMS, microfluidic chips or sensors, resulting in medical devices able to sense, interpret and even act. A lot of medical electronic devices are currently under development, while many medical conditions are still waiting for a well-designed, safe and effective electronic solution.

The development needed to introduce an electronic device successfully into the medical market differs strongly from the needs for consumer electronics. Due to the large implications device failure can have in the medical world, these devices need to be very safe and effective, which should be considered from the very first phase of device development. Special requirements exist for medical devices with close body contact, such as biocompatibility, sterilization and packaging of the device. Furthermore, the obligatory premarket approval process requires medical device testing for safety, including biological evaluation and MRI safety. Dedicated test protocols for medical devices are not always existing, making correct and efficient testing a challenge. In order to manufacture an electronic device successfully for the medical market, profound risk analysis processes and preventive/corrective measures are essential during the whole lifecycle of the device, starting at the early development stages and not finishing before a device is used with great satisfaction in the medical world.

Electronic engineers discover the medical world, and medical scientists discover electronics... a challenging marriage!

The market of (active) medical devices is highly regulated, you have to adhere to these regulations.

The emphasis should be on designing, manufacturing and distributing ôsafeômedical devices.

CE marking, classification, etcé is not a free choice. Choose and contact a Notified Body in an early stage. Choose a órespectedôNotified Body as he is your partner for long time.

If you do not achieve a CE certificate for your active medical device you are not allowed to put devices on the EU market! Even if a CE certificate is some days too late due to some administrative reason, you will have to delay market introduction. Keep your technical file/documentation up to date.

In case of incorrect certification the company is responsible for its medical devices and the certification and as such is liable.

Manage the complexity and focus on reliability of your medical devices and the electronics within:

- Design Control:
  - Know the relevant standards.
  - Establish good specifications and product definition.
  - Pay attention to project planning and management
  - Perform risk assessment and FMEA
  - Documentation : Technical file, design history file

- Verification & validation:
  - Verification and validation is a very important tool to get the right product right.
  - Review product definition, specification and derived test plans as early as possible
  - Keep documentation and test plans up to date (changes)
  - Perform tests throughout the design phase (module tests, integration test,...)

- Design with attention for DfX:
  - Save on redesign
  - Higher production yields
  - Lower field call rate
  - Lower overall cost (e.g. assembly)

- Monitor your suppliers & subcontractors (qualify, audit):
  - Specifications, changes, technology,...
  - Traceability
  - Quality & procedures

- Preventive risk management
  - Evaluate all changes (also those out of direct control e.g. legislation, supply,...)

Glossary

AC: Alternating Current, the alternating flow of electric charge
AIMD: Active Implantable Medical Device
AIMDD: Active Implantable Medical Devices Directive 90/385/EEC
AOI: Automatic Optical Inspection
ASTM: American Society for Testing and Materials
BGA: Ball Grid Array package
BOM: Bill of Material, components list
C&C: Creepage and Clearance
CAPA: Corrective Action and Preventative Action
CA: Competent Authority
CAF: Conductive Anodic Filament
CE: Communauté Européenne, French for "European Community"
cEDM: center for Electronics Design and Manufacturing
CDRH: Center for Devices and Radiological Health
cGMP: Current good manufacturing practices
CTE: Coefficient of Thermal Expansion
DC: Direct Current, the unidirectional flow of electric charge
DfA: Design for Assembly
DfM: Design for Manufacturing
DfR: Design for Reliability
DfT: Design for Testability
DfX: Design for X, where X stands for different items like testability, reliability, cost, etc.
EC: European Community
EDM: Electronics Design and Manufacturing
E.E.A.: European Economic Area market
EFTA: European Free Trade Association
EMC: Electromagnetic Compatibility
EMS: Electronics Manufacturing Services
ENIG: Electroless Nickel Immersion Gold surface plating
ESD: ElectroStatic Discharge
ETO: Ethylene Oxide
EU: European Union
EUT: Equipment Under Test
FAGG / AFMPS / FAMHP: Federal Agency for Medicines and Health Products
FB: Foreign Body
FBR: Foreign Body Reaction
FDA: Food and Drug Administration.
FMEA: Failure Mode and Effect Analysis
GENEESS: ñGEzonder door Nano-Elektronica En Slimme Specialisatieò, healthier by nanoelectronics and smart specialization
GCP: Good Clinical Practice
GLP: Good Laboratory Practice
HDE: Humanitarian Device exemption
IC: the Integrated Circuit, the chip
IDE: Investigational Device Exemptions
IEC: International Electrotechnical Commission
IMRSER: Institute for Magnetic Resonance Safety, Education and Research
iNEMI: iNternational Electronics Manufacturing Initiative
IPC: Association Connecting Electronics Industries, an international trade association for the printed board and electronics assembly industries
ISO: International Organization for Standardization
IVDD: In Vitro Diagnostic Directive 98/79/EC

kGray: Dose of gamma radiation
LED: Light-Emitting Diode
MD: Medical Device
MDD: Medical Devices Directive 93/42/EEC
MDEG: Medical Devices Expert Group - The MDEG is a group of Member States, industries and other stakeholders' representatives for the implementation of the MD directives.
MEDDEV: Commission Guideline relating to medical devices directives - the MEDDEV aim at promoting a common approach by Member States, manufacturers and Notified Bodies and are carefully drafted through a process of consultation with various interested parties
MEE: Medical Electrical Equipment
MEMS: Micro-Electro-Mechanical systems
MRI: Magnetic Resonance Imaging
MSL: Moisture Sensitivity Level, part of the packaging and handling precautions for some semiconductors
NiAu: Nickel Gold
PCB: Printed Circuit Board
PBA: Printed Board Assembly, a PCB with components mounted
PMA: Premarket Approval
PMN: Premarket Notification, also called 510k
PSU: Power Supply Unit
Q: Quality
QFN: Quad-Flat No-leads package
QM: Quality Management
QMS: Quality Management System
QS: Quality System
QSR: Quality System Regulation
R&D: Research and Development
RF: Radio Frequency
RoHS: Restriction of Hazardous Substances
SMD: Surface Mounted Device
SnPb: Tin/lead solder
Ti :Titanium
TSOP: Thin Small Outline Package
USP: United States Pharmacopeia
V&V: Verification and Validation
WL-CSP: Wafer Level Chip-Scale Package

Center for Electronics Design & Manufacturing

Kapeldreef 75
B3001 Heverlee
tel: +32-16-281282
edm@imec.be - www.cedm.be

Comments, corrections or suggestions can be send to:
Filip Ponsaerts, Filip.Ponsaerts@imec.be.